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# AMERICAN HEART JOURNAL

## For the Study of the CIRCULATION

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Contents on Inside Cover

# American Heart Journal

## CONTENTS FOR DECEMBER, 1948

### Original Communications


Report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction. Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D., New York, N. Y. ..... 891

Some Effects of Quinidine Sulfate on the Heart and Circulation in Man. M. Irené Ferrer, M.D., Réjane M. Harvey, M.D., Lars Werkö, M.D., David T. Dresdale, M.D., André Cournand, M.D., and Dickinson W. Richards, Jr., M.D., New York, N. Y. ..... 816

II. Correlation of Electrocardiographic and Pathologic Findings in Large Anterolateral Infarcts. Gordon B. Myers, M.D., Howard A. Klein, M.D., and Tomiharu Hiratzka, M.D., Detroit, Mich. ..... 838

An Experimental Study of Acute Pulmonary Arterial Obstruction, With Special Reference to the Precordial Electrocardiogram. Jack Flasher, M.D., Hiram E. Essex, Ph.D., and Arlie R. Barnes, M.D., Rochester, Minn. ..... 882

The Oxygen Content of Coronary Venous Blood as Affected by Anoxia and Cytochrome C. James E. Eckenhoff, M.D., and Joseph H. Hafkenschiel, M.D., Philadelphia, Pa. ..... 893

A Portable Electrical Manometer Suitable for Continuous Indication of Peripheral Venous Pressures. Albert A. Pollack, M.D., and Earl H. Wood, M.D., Ph.D., Rochester, Minn. ..... 899

Can the Longitudinal Anatomical Axis of the Ventricles be Estimated From the Electrocardiogram? Albert Hyman, M.D., New Orleans, La., R. B. Failey, M.D., Cincinnati, Ohio, and Richard Ashman, Ph.D., New Orleans, La. ..... 906

Evaluation of the Precordial Leads of the Electrocardiogram in Obesity. Harry L. Jaffe, M.D., Eliott Corday, M.D., and Arthur M. Master, M.D., New York, N. Y. ..... 911

Electrocardiographic Changes During Anthiomaline Treatment of Schistosomiasis. Ramón M. Suárez, M.D., Dwight Santiago-Stevenson, M.D., and Federico Hernández-Morales, M.D., San Juan, P. R. ..... 923


### Clinical Reports


Bacterial Endocarditis. Richard C. Cecil, M.D., Carl P. Parker, Jr., M.D., and William B. Porter, M.D., Richmond, Va. ..... 934

Coronary Occlusion With Myocardial Infarction Following Cholecystectomy for Relief of Anginal Pain in a Patient With Cholelithiasis. Oscar Roth, M.D., New Haven, Conn. ..... 939


### Abstracts and Reviews


Selected Abstracts ..... 943


### American Heart Association, Inc.


American Heart Association, Inc. ..... 957


### Index


Index ..... 961



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American Heart Journal

VOL. 36 DECEMBER, 1948 No. 6

## Original Communications

# REPORT OF THE COMMITTEE FOR THE EVALUATION OF ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

### (A PROGRESS REPORT ON THE STATISTICAL ANALYSIS OF THE FIRST 800 CASES STUDIED BY THIS COMMITTEE)

IRVING S. WRIGHT, M.D., CHARLES D. MARPLE, M.D., AND DOROTHY FAHS BECK, PH.D.
NEW YORK, N. Y.

THE possibility of preventing the extension of coronary thromboses and the development of mural thrombi in the presence of myocardial infarction by the use of anticoagulants was suggested by Solandt, Nassim, and Best[1,2] in 1938. These investigators were able to prevent the development of both coronary thrombi and of intracardiac mural thrombi, under conditions in which such thrombi are usually produced experimentally in animals, by the use of the anticoagulant, heparin. Their observations were not applied to man on any significant scale because of the difficulties and the risk felt to be inherent in the use of heparin clinically. In the years 1945 and 1946, Wright,[3] Nichol and Page,[4] and Peters, Guyther, and Brambel[5] reported encouraging results following the use of the anticoagulant, Dicumarol, in the treatment of coronary thrombosis with myocardial infarction in man. These reports were preliminary in nature since only small numbers of cases were studied. However, the uniformly favorable results appeared to justify a more extensive study of the use of anticoagulants in the treatment of coronary thrombosis.

---

The findings of this Committee, the result of a joint research project sponsored by the American Heart Association, are being presented jointly by the American Heart Journal and the Journal of the American Medical Association.

This study has been supported by grants from the United States Public Health Service.

Presented at the Twenty-first Annual Scientific Meeting of the American Heart Association, Chicago, Ill., June 18 and 19, 1948.

Accordingly, in the spring of 1946, the Board of Directors of the American Heart Association authorized the formation of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction. This committee is composed of internists with special interest in cardiovascular diseases who are associated with the sixteen hospitals which have contributed cases to this study. Workers in several additional institutions have participated in an advisory or consulting capacity. The participating hospitals and the responsible investigators are as follows:

*Participating Hospitals*

| | |
|---|---|
| Bellevue Hospital, New York | John E. Deitrick, M.D. |
| Beth Israel Hospital, Boston | Herrman L. Blumgart, M.D. |
| Bronx Veterans Hospital | Louis A. Kapp, M.D. |
| Cincinnati General Hospital | Johnson McGuire, M.D.<br>Helen Glueck, M.D. |
| Cleveland City Hospital | Roy W. Scott, M.D. |
| Henry Ford Hospital, Detroit | F. Janney Smith, M.D. |
| Jackson Memorial Hospital, Miami | E. Sterling Nichol, M.D. |
| Lakeside Hospital, Cleveland | Joseph Hayman, Jr., M.D.<br>Harold Feil, M.D. |
| Massachusetts General Hospital | Howard B. Sprague, M.D. |
| Michael Reese Hospital, Chicago | Louis N. Katz, M.D. |
| Mount Zion Hospital, San Francisco | John J. Sampson, M.D. |
| Pennsylvania Hospital, Philadelphia | Joseph B. Vander Veer, M.D. |
| Peter Bent Brigham Hospital | Samuel A. Levine, M.D. |
| Rhode Island Hospital, Providence | Frank B. Cutts, M.D. |
| San Francisco County Hospital | John J. Sampson, M.D. |
| The New York Hospital | Irving S. Wright, M.D.<br>Harold J. Stewart, M.D. |

*Consultants*

| | |
|---|---|
| Ralph S. Overman, Ph.D. | Grace Goldsmith, M.D. |
| Charles E. Brambel, Ph. D. | Marjorie Bellows, Ph.D. |
| Nelson W. Barker, M.D. | |

*Central Laboratory*

Irving S. Wright, M.D., Chairman of Study
Charles D. Marple, M.D., Coordinator
Dorothy F. Beck, Ph.D., Statistician

Each investigator has been assisted by a team of residents, fellows, and associates from his staff. Full credit must be accorded each of these workers whose whole-hearted cooperation has been indispensable to the success of this study. It is a pleasure to report that 1,000 patients with coronary occlusion and myocardial infarction have been studied under the conditions of this investigation.

## PLAN OF THE STUDY

Slightly fewer than one-half of these 1,000 patients have been treated by conventional methods of therapy alone. The others have been treated with anti-

coagulants, in addition to conventional methods. A record of each case has been prepared in detail on master forms by the responsible investigator and his associates and forwarded to the Central Office of the Committee at The New York Hospital. The master forms are being subjected to intensive statistical analysis and a definitive report on the 1,000 cases will be prepared as promptly as the analysis will permit. The present report includes data obtained from analysis of the first 800 cases reported to the Central Laboratory. Although it is possible that the addition of the last 200 cases, and other later revisions, may change the figures somewhat, it is unlikely that the conclusions will be altered significantly since the relationship of the control and treated groups as to deaths and thromboembolic complications has remained relatively stable as the sample has increased in size.

Three hundred sixty-eight patients admitted to the participating services on *even* days received conventional therapy and constitute "the control group." Four hundred thirty-two patients admitted on *odd* days received anticoagulants in addition to conventional therapy and constitute "the treated group."

The principles used as guides in the administration of Dicumarol and heparin were as follows:

a. Heparin may be given for the first forty-eight hours or more, if desired.

b. Prothrombin determinations are to be done each day and no Dicumarol should ever be ordered unless the morning prothrombin report is available.

c. Dicumarol, 200 to 300 mg. daily, should be given until the prothrombin time is 30 seconds.

d. Dicumarol, 50 to 100 mg. daily, should be given if the prothrombin time is between 30 and 35 seconds.

e. Dicumarol is withheld if the prothrombin time is 35 seconds or more. Then, no drug is given until the prothrombin time is again down to 30 seconds or less, after which the drug is again given cautiously in 100 mg. doses.

f. The Link-Shapiro technique, using undiluted whole plasma, or the Quick method is to be used for determining the prothrombin clotting time and it is suggested that the Link-Shapiro method, using 12.5 per cent diluted plasma, be employed as an additional check or safeguard. All prothrombin times are given in terms of the Link-Shapiro (undiluted) method.

g. Unless contraindications arise, the Dicumarol therapy is to be continued in the chosen cases over a minimum period of thirty days; preferably thirty days after the last thromboembolic episode.

h. In instances of hemorrhagic manifestations, the use of synthetic vitamin K preparations in doses of 60 to 75 mg. and transfusions of fresh whole blood (may be citrated) are recommended.*

A comparison of the patients in the "control" group with those in the "treated" group shows a striking similarity with regard to age, history of previous infarction, and estimated severity of the present attack, as shown in Table I. The average age of the control group was 60 years; that of the treated group, 59 years. The average age of men in the control group was 58.9 years, and in the treated group, 57.2 years. The average age of women in the control group was

*From the instructions issued to each participating team (slightly modified).

64.1 years, and in the treated group, 64.6 years. In this series of 800 cases, the average age of female patients was approximately 6.4 years greater than that of male patients.

TABLE I. COMPOSITION OF SAMPLE. TOTAL GROUP: 800 CASES OF CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION SURVIVING FIRST DAY OF HOSPITALIZATION

| ITEM COMPARED | CONTROL GROUP (EVEN DAYS) | TREATED GROUP (ODD DAYS) |
|---|---|---|
| Number of cases | 368 | 432 |
| Average age | 60 years | 59 years |
| Proportion males | 77% | 76% |
| One or more previous infarctions | 24% | 22% |
| Illness "severe" at onset | 23% | 30% |
| Anticoagulant therapy received (exceptions as noted) | 88% no anticoagulants<br>12% some anticoagulants (primarily after complications) | 81% Dicumarol without heparin<br>14% Dicumarol plus some heparin<br>3% no anticoagulants because of renal or liver disease or hemorrhage<br>2% no anticoagulants because of miscellaneous errors |

Analyzing the two groups for a history of one or more previous myocardial infarctions, it was found that 24 per cent of the control group and 22 per cent of the treated group had had one or more previous infarctions.

An estimate of the severity of the attack was made for each patient at the time of diagnosis and recorded as mild, moderate, or severe. Twenty-three per cent of the control group and 30 per cent of the treated group were classified as having severe attacks. Although this classification is admittedly arbitrary, the results suggest that the treated group contains a somewhat greater proportion of severely ill patients. The control and treated groups were also closely similar when the medical histories of cardiovascular diseases and the locations of their original infarcts were compared.

Eight-eight per cent of patients in the control group received no anticoagulant, but 12 per cent did receive some anticoagulant therapy, often for short periods only. Anticoagulants were administered to patients in the control group following the development of a thromboembolic complication because of pressure on the part of the family or a private physician* or for miscellaneous reasons. Of the treated group, 81 per cent received Dicumarol only, while 14 per cent received Dicumarol and some heparin. In three per cent of the "treated cases" no anticoagulants were given because of concurrent renal or hepatic disease or because of hemorrhagic conditions, and 2 per cent received no anticoagulant because of miscellaneous errors.

In the computation of the rates of incidence upon which all of the following charts are based, small and conservative corrections were made in order to simplify

*This factor became intensified as the study progressed.

the presentation. In the control group the rates are corrected for exceptions to the "no anticoagulant" rule. Rates as shown are those it is estimated would have occurred if no patient in the control group had received any anticoagulant. They differ only slightly from the data as actually reported and are believed to present a truer picture of rates without anticoagulants. In the treated group the rates are corrected for erroneous omissions of anticoagulants. There is evidence that with more intensive and inclusive anticoagulant therapy, the rates for death and complications in the treated group would have been lower than those shown. No correction was made for those patients from whom anticoagulants were withheld because of specific contraindications. These omissions are considered to be disadvantages inherent to this type of therapy.* In both groups all rates for thromboembolic complications and hemorrhagic manifestations, as stated in this interim report, refer to conditions diagnosed clinically. Statistics based on autopsy findings are not yet available, but are being analyzed at this time.

## RESULTS

Fig. 1 illustrates the contrast between the death rates in the control group and in the group who received anticoagulant therapy. Twenty-four per cent of the control patients died, whereas 15 per cent of the treated patients died. Thus, somewhat more than one-third of the individuals who would have died without anticoagulant therapy survived the specific attack under consideration when anticoagulants were given. This difference is statistically significant.† Further examination indicates that the greatest improvement was achieved in patients who had suffered one or more thromboembolic complications prior to death. Such deaths occurred in roughly 10 per cent of the control cases, but in only 3 per cent of the treated cases. Death, not preceded by a clinically recognized thromboembolic complication, occurred in approximately 14 per cent in the control group as against 12 per cent in the treated group. As previously anticipated, anticoagulants reduced the death rate largely by reducing the incidence of those thromboembolic complications which, directly or indirectly, result in death.

---

*These corrections were made by it being assumed that if anticoagulants had been completely withheld from all control patients receiving anticoagulants, they would have developed at least as many further complications and would have died at least at the same rate as did control patients of comparable age who received no anticoagulants at any time under approximately comparable circumstances. If actual rates for subgroups among these patients for whom exceptions were made did not already exceed these estimates, the estimates were substituted for the actual data for these particular subgroups. An appropriate modification of this correction procedure was applied in the case of the treated group and for hemorrhagic manifestations in both groups. The resulting corrected figures are portrayed graphically and referred to in the text without reference to the corrections or to the exceptions in treatment. *The corrections for exceptions proved to be small and sometimes were completely without effect on the rates. They do not alter at any point the basic differences between the groups from which conclusions are drawn.*

†The term statistically significant is used throughout the text to mean that the chances that two random samples from the same population would yield, on the basis of chance alone, differences as great as those observed and in the same direction are less than one in one hundred. In most instances the chances of obtaining these differences in two samples from the same universe are, in fact, very much less than one in one hundred: in the case of thromboembolic complications, they are less than one in one thousand.

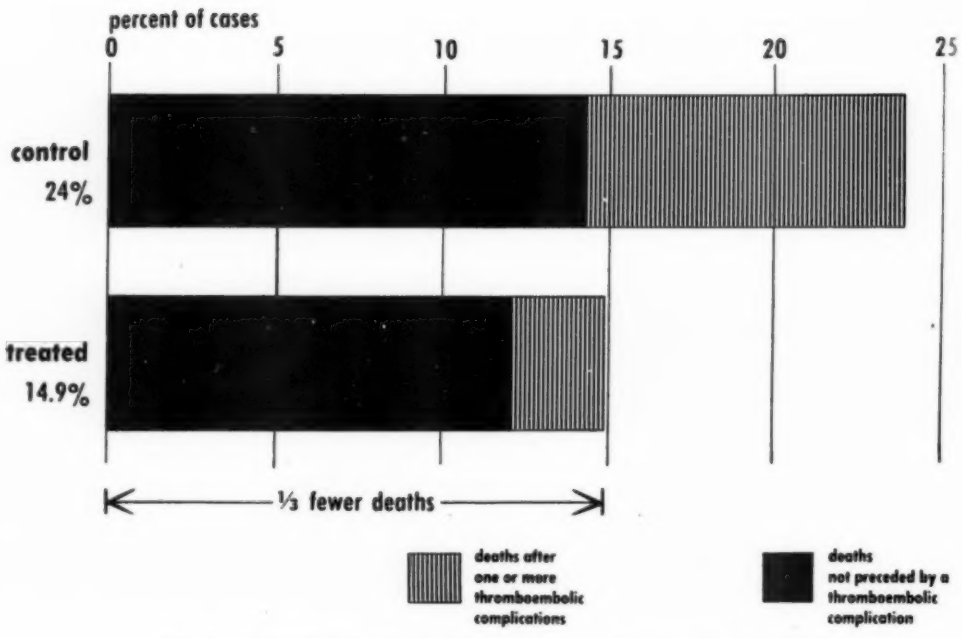


Fig. 1.—Patients dying in the control and treated groups under study.

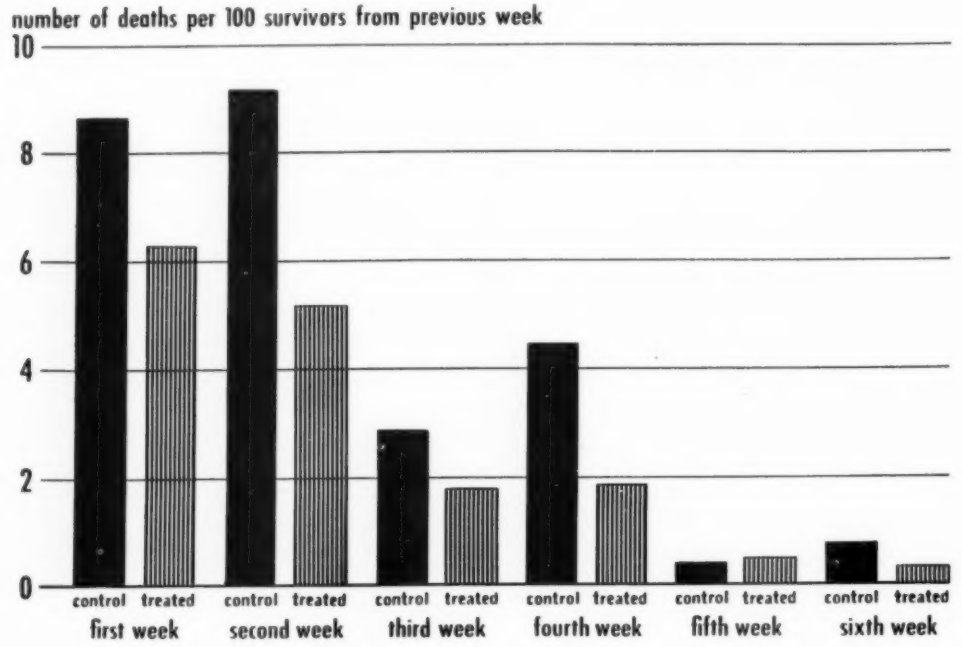


Fig. 2.—Comparison of death rates by week of illness in the control and treated groups.

The death rates by week of illness, as shown in Fig. 2, were highest during the first two weeks, but were still considerable during the third and fourth weeks. For each period the death rate for the control patients was found to be significantly greater than that for the treated group. These figures indicate, first, that anticoagulant therapy, if not used before, should be begun as late as the second or third week after a myocardial infarction has occurred, or later if complications have developed, and, second, that to give maximal protection, anticoagulant treatment should be continued for at least four weeks after the last thromboembolic episode.

Fig. 3 presents the death rates by major age groups. The greatest benefits in the reduction of mortality are in patients 60 years of age or older. These statistics show that the therapeutic effect of anticoagulants is sufficiently important to justify their use in the older age groups. Hemorrhagic complications have been so few and so mild throughout the entire study and the benefits of treatment of the older age groups are so pronounced that we do not hestitate to prescribe anticoagulants to older patients. It should be recognized, however, that older patients have a higher incidence of unrelated complications and that careful consideration of such factors is mandatory. While the crude death rates for patients under the age of 59 years in both the treated and the control groups did not show a significant difference, it will be seen in Fig. 6 that the incidence of thromboembolic complications is high in these age groups, and that the treated patients show a much lower incidence of thromboembolic complications. Such thromboembolic complications may not only be serious incidents in themselves, but they may result in such serious permanent disabilities as hemiplegia (following cerebral emboli), chronic venous insufficiency (following thrombophlebitis), or residual myocardial damage (following repeated myocardial infarction).

Fig. 4 shows the percentage of patients developing one or more thromboembolic complications. Twenty-five per cent of the control patients, in contrast to only 11 per cent of the treated patients, developed at least one such complication. This difference is statistically significant. However, of these treated patients, 3.5 per cent developed their first complication before they had received an anticoagulant* and 1.5 per cent developed their first thromboembolic complication during the first three days of anticoagulant therapy, a stage of treatment in which Dicumarol is ordinarily not fully effective. Thus, 5 per cent developed thromboembolic complications when anticoagulant therapy *could not* have been significantly effective and only 6 per cent developed thromboembolic complications while they were actually under the therapeutic effect of anticoagulant therapy.

The number of thromboembolic complications per one hundred cases is presented in Fig. 5. Among each 100 cases in the control group, thirty-six thromboembolic complications were diagnosed clinically, whereas among each 100 cases in the treated group, only fourteen thromboembolic complications were so diagnosed. In other words, patients in the "treated group" experienced slightly more than one-third as many thromboembolic complications as did patients in the control group, a contrast that is again highly significant statistically. This

*Included in this group are those who never received anticoagulants because of contraindications.

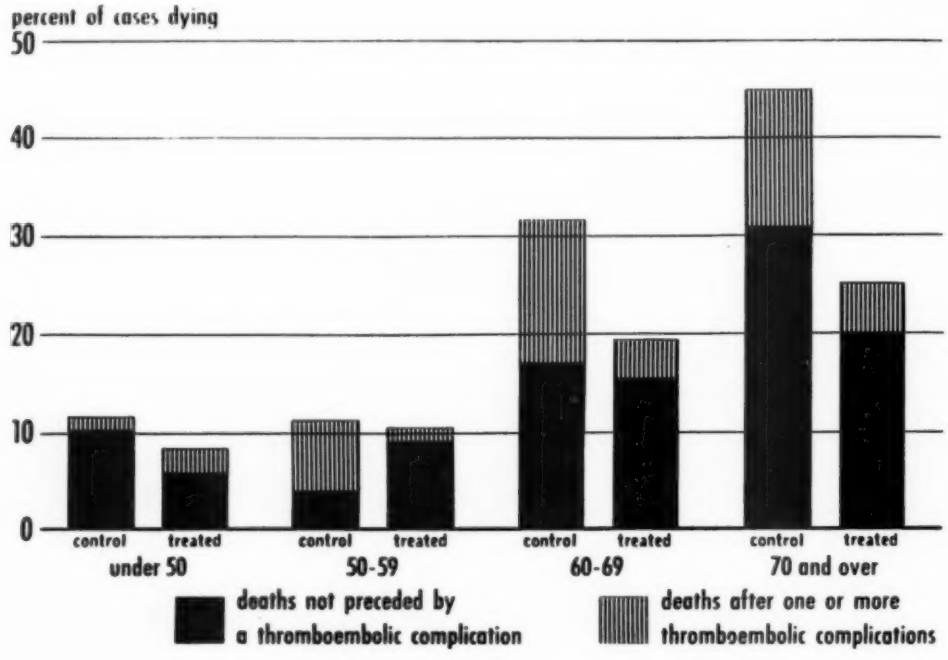


Fig. 3.—Death rates by age groups in the control and treated groups.

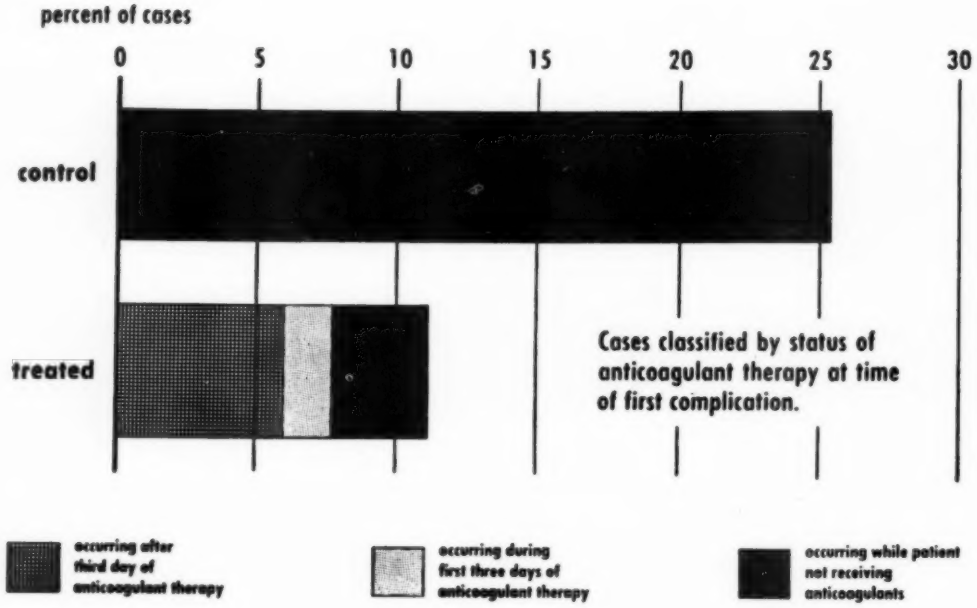


Fig. 4.—Patients developing one or more thromboembolic complications.

contrast is further emphasized by the following facts: It is noted that five thromboembolic complications per 100 cases developed while the patients were not receiving anticoagulant therapy and 2.5 thromboembolic complications per 100 cases developed during the first three days of anticoagulant therapy, when Dicumarol is not considered efficacious. Actually, then, only 6.5 thromboembolic complications per 100 treated cases occurred in patients who were under the full therapeutic effect of anticoagulant therapy. This figure includes complications in some patients whom we would not now consider to have been under adequate therapy at the time the complication occurred. Autopsies were conducted on 48 per cent of the patients dying among the 800. The autopsy records for these cases are being studied intensively and will yield further light on the effects of anticoagulant therapy on thromboembolic complications.

The highest incidence of thromboembolic complications among the control cases occurred in the age group between 50 and 59 years (Fig. 6); this is in distinct contrast to the death rate by age groups (Fig. 3). The explanation for this contrast may be that while the younger patients suffer numerous thromboembolic complications and while some of these complications result in serious damage, the younger patients are able to survive them. Thus, an individual under the age of 60 years may have three or four thromboembolic complications without a fatal episode, whereas an older patient may succumb to the initial attack and hence not have the opportunity of developing repeated thromboembolic attacks. This chart clearly indicates the value of anticoagulant therapy in preventing thromboembolic complications in all age groups. Within the treated group, a distinction is made between those actually receiving anticoagulants and those who were not receiving anticoagulants at the time of their thromboembolic complications. This further emphasizes the effects of anticoagulant therapy.

In Fig. 7 the rate of thromboembolic complications by week of illness is considered. The advantage in using anticoagulants is clearly demonstrated for each of the first four weeks of the illness. As is the case with deaths, the incidence of thromboembolic complications is highest in the second week, but is marked throughout the first four weeks. This again clearly indicates the importance of beginning anticoagulant therapy even as late as the second or third week following a myocardial infarction. Since it is impossible to predict from the condition of the patient during the first week whether he will develop thromboembolic complications during subsequent weeks or whether he will die from them, it is important to give anticoagulant therapy to all patients with coronary occlusion and myocardial infarction unless specific contraindications exist.

Fig. 8 indicates the types and locations of thromboembolic complications as they were encountered, and the effects of anticoagulant therapy in each group. Under the classification of secondary myocardial infarctions, there was evidence of extension of the original thrombosis in nine cases per 100 in the control series as against two cases per 100 in treated patients. There was infarction of new areas in the myocardium in 6.5 cases per 100 in the control series as against 2.5 among treated patients. Pulmonary emboli occurred in 9.4 cases per 100 among the control group as against 5.2 cases among the treated patients. More-

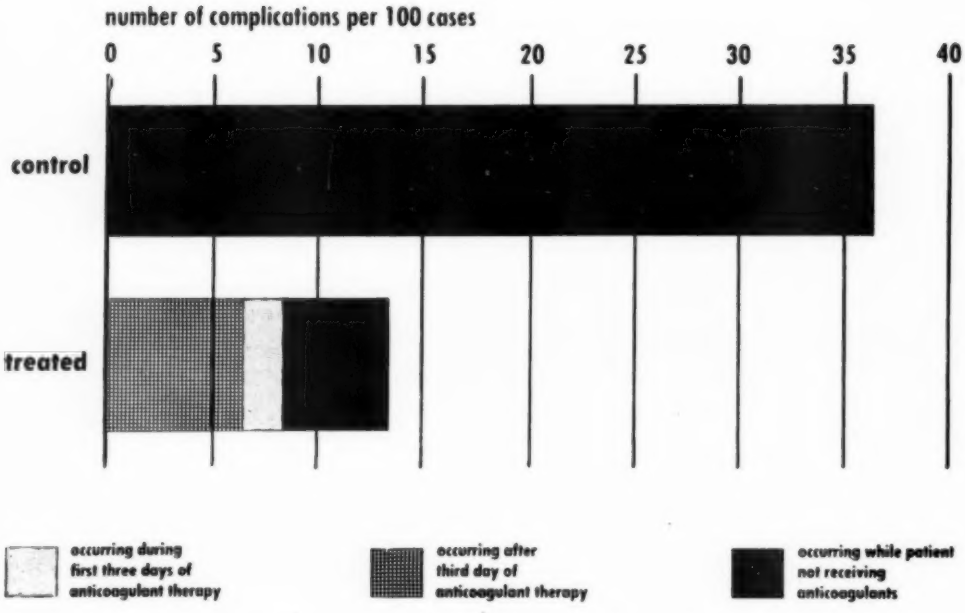


Fig. 5.—Number of thromboembolic complications in the control and treated groups.

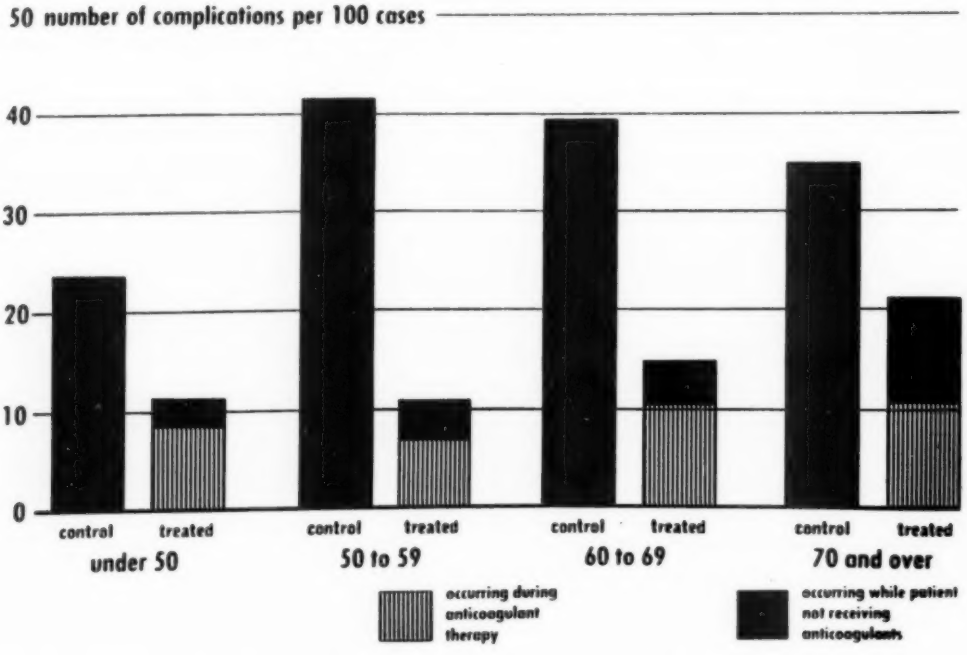


Fig. 6.—Rates of thromboembolic complications by age groups.

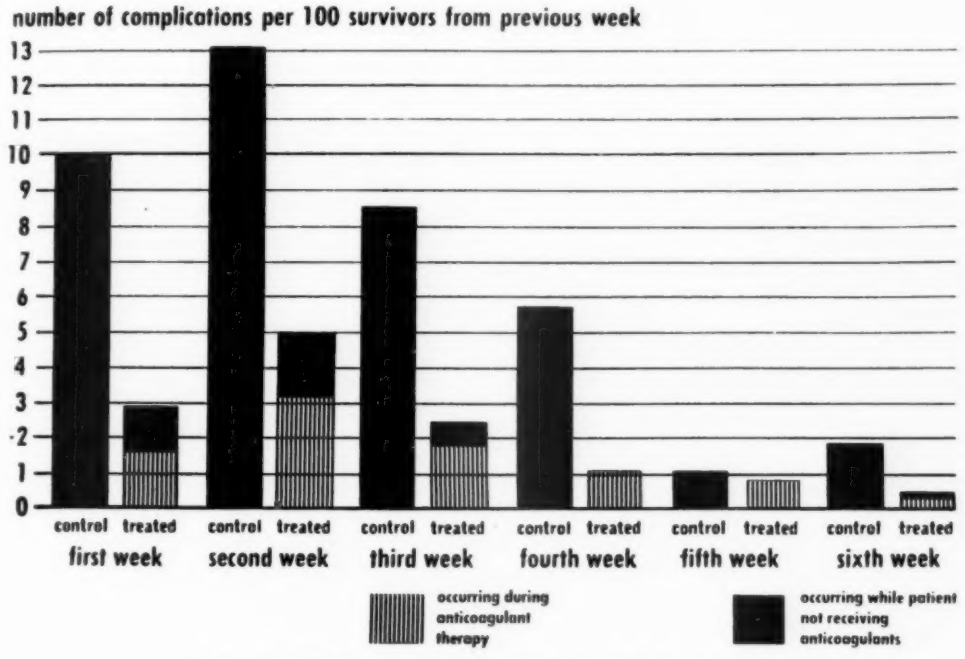


Fig. 7.—Rates of thromboembolic complications by week of illness.

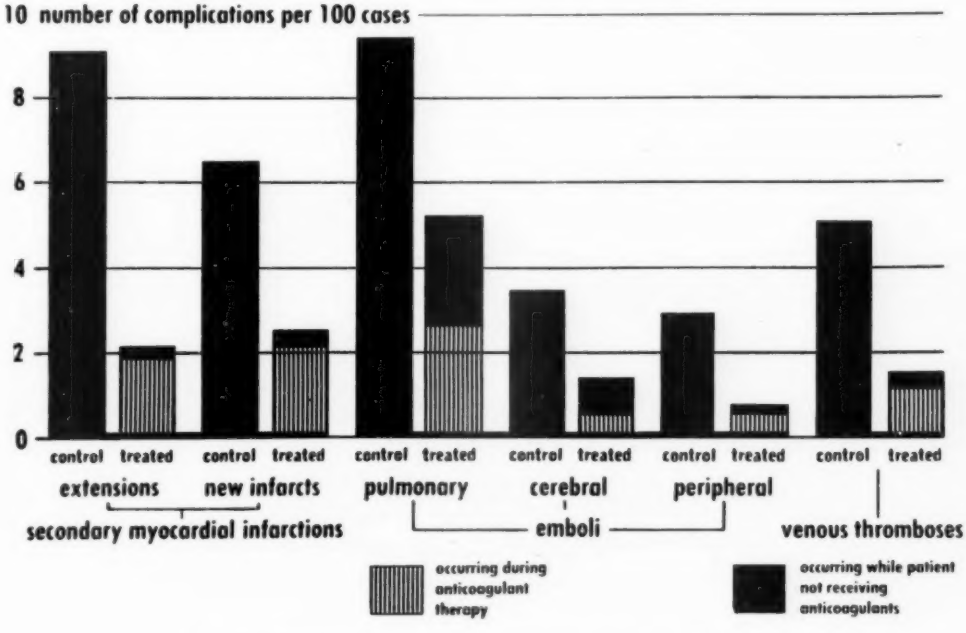


Fig. 8.—Types and locations of thromboembolic complications.

over, one-half of the so-called treated patients were not actually receiving anticoagulant therapy at the time they suffered their pulmonary embolism. Cerebral emboli occurred in 3.4 cases per 100 of the control patients as against 1.4 cases per 100 among the treated patients. Peripheral emboli developed in 3 cases per 100 of the control group as against 1 per 100 of the treated patients, and venous thromboses occurred in 5 cases per 100 of the control group as against less than 2 per 100 of the treated patients. Hence, it will be seen that at every site and with every type of complication, those receiving anticoagulant treatment in addition to conventional therapy had a distinctly better chance of escaping thromboembolic complications than those who received the conventional forms of therapy only.

The hazard of hemorrhagic manifestations resulting from anticoagulant therapy has been carefully reviewed (Fig. 9). It should be noted that hemorrhagic manifestations unrelated to anticoagulants numbered 6 per 100 cases in the control group. This is in comparison to a rate of slightly more than 12 per 100 cases among those patients who were classified as "odd day" or "treated" patients. It should be noted, however, that of these complications in the latter group, two in twelve developed in patients who were not under anticoagulant therapy when their hemorrhages occurred. In an additional three, the hemorrhages were known to have been the result of causes other than anticoagulants and not to have been aggravated by that therapy. The total hemorrhagic manifestations in the treated group which are known to have been the result of causes other than anticoagulants approached that found in the control group. An additional 7 per 100 cases, however, were believed to have been due to, or aggravated by anticoagulants. The incidence of severe hemorrhages resulting from anticoagulant therapy was extremely low. Of the thirty such hemorrhages clinically observed, fifteen (50 per cent) were mild in severity, fourteen (47 per cent) were moderately severe, and only one (3 per cent) was severe. The autopsy findings bearing on hemorrhagic phenomena are not yet ready for presentation, but those examined to date present no alarming picture of the hemorrhagic risks in anticoagulant therapy under proper controls. Blumgart and his co-workers,[6] working with dogs whose coronary arteries had been ligated, found that dicumarolized animals (in some instances with prothrombin times of 132 seconds) showed no increase of hemorrhages in the myocardium, endocardium, or pericardium when compared with nondicumarolized animals.

The sources of bleeding in relation to anticoagulants is demonstrated in Fig. 10. There is a definite incidence of hemorrhage among the control group in each of the categories except that for epistaxis. Hemorrhages due to causes other than anticoagulants also occur in three of the categories in the treated group. It will be noted that hemorrhages occurred more frequently in the treated group in all categories except that of hemoptysis. The explanation for the greater incidence of hemoptysis in control patients is that pulmonary infarction is much more common among these patients than among the treated patients.

The records of patients who received anticoagulant therapy and yet developed thromboembolic complications or died are being subjected to analysis in the Central Laboratory. It appears, on the basis of present experience, that

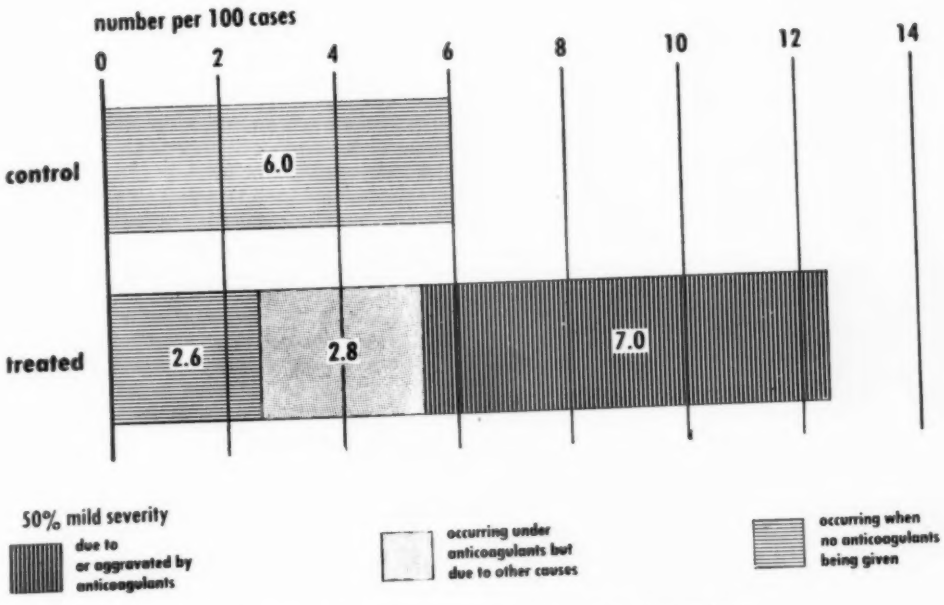


Fig. 9.—Relations of hemorrhagic manifestations to anticoagulants.

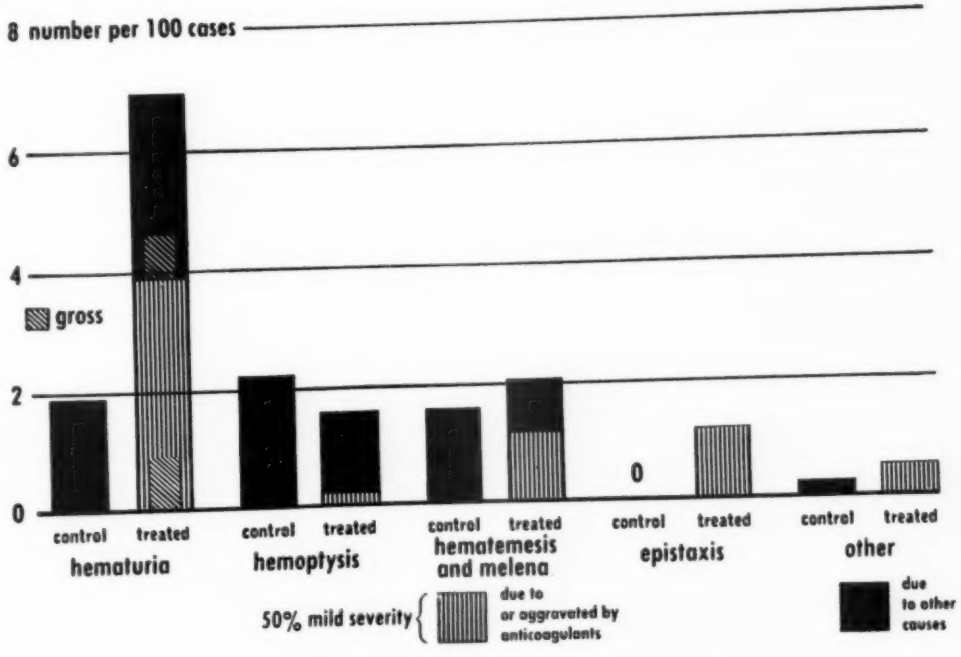


Fig. 10.—Sources of bleeding in hemorrhagic manifestations.

a considerable proportion of the failures occurred because the prothrombin time was not adequately prolonged. While there is at present a question as to what constitutes the minimal effective prothrombin time, it is our experience that a safe and effective therapeutic range is between 30 and 50 seconds by the Link-Shapiro modification of Quick's one-stage method. This range, as interpreted in our laboratory, would approximate a prothrombin activity of between 20 and 10 per cent. For heparin, the clotting time should be approximately three times normal. Although statistical evidence as to the relative incidence of thromboembolic complications at various prothrombin times (that is, at various levels of reduced prothrombin activity) is not yet available, a review of those cases in which thromboembolic complications occurred during the administration of Dicumarol reveals that of the thirty-eight complications* occurring under these conditions, only four occurred in patients whose prothrombin time is known to have been maintained at levels of 30 seconds or more for at least the three days preceding the appearance of the complication. Further analyses regarding this factor will be recorded in forthcoming publications. It is not sufficient to state that a patient has received anticoagulant therapy. Key questions which must be answered are: how much Dicumarol has been administered, and for how long; what levels of prothrombin time were obtained, and how consistently were these maintained? With this information it should usually be possible in the future to determine whether a failure was the responsibility of the drug or of those administering it.

## SUMMARY

This report summarizes the results obtained by a preliminary statistical analysis of the first 800 cases studied by the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction. In the analysis the incidence of deaths and of both thromboembolic and hemorrhagic complications has been compared in a "control" series of patients treated by conventional methods alone and in a series of "treated" patients who received anticoagulants (Dicumarol, heparin, or both) in addition to conventional therapy. The composition of the two groups was found to be essentially the same.

The rates of deaths and the number of thromboembolic complications per 100 cases have been calculated for the control and treated groups as a whole, by week of illness, by age of patient, and by type and location of the specific thromboembolic complication. The percentage of patients developing one or more complications has also been analyzed. The results in every category studied indicate that the use of anticoagulants improves strikingly the outlook of the patient suffering a coronary occlusion with myocardial infarction.

The incidence of hemorrhagic manifestations was also analyzed. It was found that about six minor or moderate hemorrhagic manifestations per 100 cases occur in patients not receiving anticoagulants. This incidence is about six per 100 higher in patients receiving anticoagulants.

*Complications for which the date is not accurately known and those occurring on days for which no prothrombin time is available are excluded from this total, but complications occurring in control cases when under anticoagulant therapy are included.

Although the minimum prolongation of the prothrombin time necessary to obtain a therapeutic effect from Dicumarol in each patient has not been established, it is our experience that a range of from 30 to 50 seconds, as measured by the Link-Shapiro modification of the Quick one-stage technique, produces a safe and an effective therapeutic level. This range of prothrombin times approximates a decrease in prothrombin activity to between 20 and 10 per cent as determined in our laboratory. In using heparin we attempt to prolong the clotting time of whole blood to approximately three times the normal value by the Lee-White technique. In only four cases of the entire series did thromboembolic complications occur when the prothrombin time had been maintained at a level of 30 seconds or above for at least three days prior to the occurrence of the complication.

## CONCLUSIONS

On the basis of data compiled from 800 cases of coronary occlusion with myocardial infarction, it is concluded that:

1. Patients treated with anticoagulant therapy in addition to the conventional forms of therapy experience a death rate and incidence of thromboembolic complications during the first six-week period following an attack which are markedly lower than those experienced by patients treated solely by conventional methods.

2. Anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists.

3. In the absence of other hemorrhagic states, the hazards from hemorrhage due to anticoagulants are not sufficient to contraindicate their use in the treatment of coronary occlusion providing there are facilities for adequate laboratory and clinical control.

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# SOME EFFECTS OF QUINIDINE SULFATE ON THE HEART AND CIRCULATION IN MAN

M. Irené Ferrer, M.D., Réjane M. Harvey, M.D., Lars Werkö, M.D., David T. Dresdale, M.D., André Cournand, M.D., and Dickinson W. Richards, Jr., M. D.
New York, N. Y.

With the development of the technique of right heart catheterization for the determination of cardiac output[1,2,3] and for the recording of right heart pressures,[4] it is possible to study the action of certain drugs on the dynamics of the circulation in man. Drugs best suited to this type of investigation are those which can be administered in a single dose and which manifest their maximum effect in one to three hours. Quinidine fulfils these criteria. Moreover, the effects of this drug on the circulation in man, aside from its action on arrhythmias, have been incompletely studied.

The pharmacology of quinidine was first described in 1893, and the drug was introduced into clinical use in 1918.[5] During the next ten years clinical and experimental investigations were primarily concerned with the effect of quinidine on auricular fibrillation and other arrhythmias and the mechanisms by which normal rhythm was restored. Some observations have been made on heart rate, blood pressure, peripheral circulation, stroke volume, cardiac output, and contractility of heart muscle. Most of these studies have been made on isolated heart preparations or on animals, but a few have been made on man. Extensive studies have been made in man on the electrocardiographic changes produced by the drug.

In human and animal experiments, Lewis and associates[6,7,8] noted that in auricular fibrillation quinidine slowed the auricular but increased the ventricular rate. In dogs with normal sinus rhythm, some observers have found an increase[9,10,11] and some, a slowing,[12] while others noted no change in heart rate.[13] Starr and co-workers[14] reported an increase in heart rate in human subjects with normal sinus rhythm.

Most investigators, using intravenous quinidine in animals, found a fall in blood pressure,[13,15-18] but one group noted a rise.[9] Levy[19] has stated that there is no significant effect on the blood pressure in man. The effect of quinidine on the peripheral circulation has been reported by two groups of investigators.[15,16] In evaluating the fall in blood pressure produced by quinidine in animals, both

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the First Medical and Chest Divisions, Bellevue Hospital, New York City.

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groups suggest an action of the drug on the peripheral vessels. In addition, Jackson and associates[15] were able to demonstrate an increase in leg volume and a fall in pulmonary artery pressure coincident with the fall in systemic blood pressure. They state, ". . . it is to be noted that the dilatation of the vessels of the hind limb with the consequent increase in volume and the dilatation of the pulmonary arterioles and capillaries both indicate that the drug possesses a distinct peripheral action on the circulation. . . ."

A diminution in stroke volume and work per beat has been reported by Starr and his co-workers.[14] They also found no significant change in cardiac output in man, using the ethyl iodide method of cardiac output determination. However, another group,[9,10] working with dogs, found an increase in cardiac output.

Most investigators have reported a weakening of the contraction of the animal heart following quinidine.[12] Cohn and Levy[13] demonstrated, by means of the myocardiograph, an increase in the amplitude of the recorded cardiac contraction.

Quinidine produces certain well-known changes in the electrocardiogram.[6,7,13,16,17,20-22] The majority of investigators describe prolongation of the Q-T interval and T-wave changes. In addition, widening of the QRS complex sometimes occurs.[17] Reports are contradictory as to the effects of the drug on the P-R interval. Prolongation of this interval was noted by Lewis and associates,[6,7] but Gold and co-workers[11,17] found that it remained the same or became shorter.

## METHOD OF STUDY

The present study is concerned with the effect of quinidine sulfate on the circulation in subjects with an essentially normal cardiovascular status and in patients with heart disease. Quinidine sulfate, 0.8 Gm. by mouth, was given in a single dose on the basis that this amount represents the maximum effective single oral dose of this drug, as originally suggested by Lewis[7] and recently re-emphasized by Gold.[23] In the treatment of arrhythmias the maximum therapeutic effect following the administration of the dose indicated was noted one and one-half to two and one-half hours after ingestion[17,23] and the plasma concentration was found to reach its height in two to four hours.[24,25] The electrocardiographic changes have been described as early as fifteen minutes after oral administration of quinidine.[22] Any circulatory effects can, therefore, be expected during the first three hours after ingestion of the drug.

Changes in the circulation were measured by the technique of right heart catheterization. The measurements obtained include right heart pressures and cardiac output, as well as peripheral artery pressures, blood volume, and electrocardiograms.

Pressure changes in the right auricle, right ventricle, and pulmonary artery were recorded by means of an intracardiac catheter attached to a Hamilton manometer.[4] Femoral or brachial artery pressures were recorded by direct intra-arterial needle and a Hamilton manometer. The systolic, diastolic, and mean pressure values represent the average figures obtained by analyzing each heart

beat during two complete respiratory cycles, as described by Bloomfield and associates[4] and more recently by Werkö.[26] Heart rate was computed from the electrocardiogram. Cardiac output and cardiac index were determined by the direct Fick principle.[2,27] Total peripheral resistance was calculated according to the formula:

$$R = \frac{(\textit{Arterial Mean Pressure Minus Right Auricular Mean Pressure}) \times 1{,}332}{\textit{Cardiac Output Per Second}}$$

and expressed as dynes, seconds, cm.$^{-5}$. Pulmonary resistance was computed using pulmonary artery mean pressure. Blood volume determinations were made by the dye method as modified by Noble and Gregersen.[28] Standard Leads I, II, and III were recorded by means of the Cambridge electrocardiograph.

## PROCEDURE

All patients studied were in the resting state. The majority were fasting, but a few took liquids two hours before the study was begun. Most of the patients received 0.1 Gm. of phenobarbital the evening before the procedure, and 0.1 to 0.2 Gm. of pentobarbital and 0.03 Gm. codeine sulfate, orally, one to two hours before any determinations were made. A test dose of 0.2 Gm. of quinidine sulfate was given the day preceding the study.

Before the introduction of the catheter or the intra-arterial needle, a control electrocardiogram (standard Leads I, II, and III) was taken. The catheter was placed with the tip in the right auricle and the brachial or femoral artery needle was inserted. At least thirty minutes elapsed with the patient at rest before control pressures were recorded. Pressure tracings were made from the right auricle, then (after the catheter tip was advanced) from the right ventricle, and in some instances, from the pulmonary artery, simultaneously with peripheral artery tracings and standard Lead II of the electrocardiogram. The control cardiac output was then determined with the catheter in the right ventricle. In the majority of cases the catheter tip was left in the right ventricular cavity for the rest of the study in order to avoid excessive manipulation. A control blood volume, by means of the ten-minute sample technique,[28] was measured.

The patient then received 0.8 Gm. of commercial quinidine sulfate by mouth. Every half hour for the next two to three hours, right ventricle and peripheral artery pressure tracings and the three standard leads of the electrocardiogram were recorded. Cardiac output determinations were done one hour and two hours after quinidine sulfate unless the tracings showed a marked fall in systemic blood pressure. In this event, cardiac output was determined immediately. The study was concluded two and one-half to three hours after the administration of the drug, with a second measurement of blood volume.

*Types of Patients Studied.*—The patients studied were of two types: (1) those with essentially normal circulation, and (2) those with cardiovascular disease. Eight normal subjects and twelve patients with heart disease were stud-

ied by the catheterization technique. Their control and postquinidine values are given in Tables II, III, IV, and V, respectively.

The criteria used for diagnosis of the cardiac patients were those adopted by the American Heart Association.[29] The functional and therapeutic evaluation represents the status of the patient at the time of the study. It became obvious, however, on examination of the control physiologic data (Tables IV and V) that, in addition, a tentative physiologic classification could be set up. This was done in an effort to place these patients in the proper perspective as far as the natural history of their disease is concerned. Variations in systemic flow (cardiac output) and right heart pressures comprise the basic criteria for the physiologic classification offered. Admittedly,[29, p. 71] the standard functional classification, based on clinical tests, is of limited accuracy in determining early abnormalities of cardiac function. This is not unexpected, as it seems logical to assume that abnormal variations in function appear at a much earlier stage in cardiac disease than do the symptoms indicative of a breakdown in functional capacity. This physiologic classification is somewhat arbitrary, but actual measurement of pressures and blood flow should provide a more accurate index of circulatory function than the clinical criteria of the standard classification.

*Group A* is composed of two patients with normal cardiac output ($3.12 \pm 0.4$ liters per minute per square meter of body surface)[2] but elevation of either systolic or diastolic right ventricular pressures (upper limit of normal values 30/5).[4]

*Group B* is represented by one patient with a high cardiac output and elevation of right ventricular systolic pressure. All of the patients in Groups A and B are those with the American Heart Association classification of I,A.

*Group C.* A patient (S. H.) with a low cardiac output and elevated right ventricular pressures, who had never received digitalis, and was classified III,C, represents Group C.

*Group D.* These four patients had been maintained on digitalis for a considerable period of time and in spite of this were still in Class III,C. All except one had low cardiac outputs and all had elevated right ventricular pressures. Although the cardiac output value of 3.18 liters per minute per square meter of body surface of Patient T. C. is within the normal range, the patient had cor pulmonale which, in its early stages, is often characterized by a high cardiac output.[3,31] Hence, this figure of 3.18 liters per minute per square meter might be construed as a low cardiac output for this cardiac condition.

*Group E.* These four patients, classed as II,B, and all well digitalized, had low or low-normal cardiac outputs and normal right ventricular pressures. In addition, two of the four showed markedly increased blood volumes. It should be stated that clinically this group of patients had had severe cardiac decompensation from which they had recovered. Apparently, therefore, the only residual dynamic defect consistently present was that of systemic flow, as the right heart pressures were normal.

As will be described, there were no changes in cardiac rhythm following quinidine administration. This study, therefore, is concerned with those effects of quinidine on the heart and circulation other than those associated with alterations in cardiac rhythm.

*The Influence of Cardiac Catheterization on Hemodynamics.*—An indwelling catheter in the right heart causes a negligible effect on the circulation.[1] For the interpretation of the results of the present study, however, it was important to have a control series of observations on subjects who went through the same procedure except for the administration of quinidine; specifically, the catheterization, the intra-arterial indwelling needle, and the period of prolonged recumbency.

Such a series was that in which a study was made of positive pressure breathing.[26,30] The procedure followed during that investigation was sufficiently similar to the one used in the present quinidine study to warrant comparison. The patients were kept three to four hours on a fluoroscopic table which was covered with a sponge rubber mattress. They received the same premedication and were also in the fasting state. Control observations on blood pressures and cardiac outputs were made at the beginning and at the end of each case study. The second determination, some two to two and one-half hours later, was always preceded by a period of absolute rest, usually twenty to thirty minutes, during which the patient was undisturbed by any manipulations. Comparison of these two sets of observations gives an indication of the variations produced by the experimental method. Results are shown in Table I. It is obvious that in the normal subjects the variation in both arterial and right ventricular pressures was small. In the majority of normal subjects there was a small rise in systolic and diastolic arterial pressures and a slight tendency toward a fall in right ventricular

TABLE I. HEMODYNAMIC CHANGES OBSERVED OVER A PERIOD OF TWO AND ONE-HALF HOURS IN A GROUP OF SUBJECTS NOT RECEIVING MEDICATION

| | RANGE OF VARIATION* DURING OBSERVATION PERIOD IN: | |
|---|---|---|
| | GROUP OF ELEVEN SUBJECTS WITH NORMAL CIRCULATION | GROUP OF EIGHT CARDIAC PATIENTS |
| Arterial blood pressures (mm. Hg) | | |
| Systolic | −9 to +13 | −3 to +38 |
| Diastolic | −4 to +11 | −1 to +15 |
| Mean | −4 to +12 | −4 to +27 |
| Right ventricular pressures (mm. Hg) | | |
| Systolic | −2 to +3 | −1 to +16 |
| Diastolic | −2 to +4 | −4 to +9 |
| Mean | −3 to +2 | −6 to +13 |
| Heart rate (beats/min.) | −15 to +10 | −3 to +15 |
| Cardiac output (per cent) | −15 to +14 | −15 to +11 |

*With respect to first control determination.

systolic and diastolic pressures. In the cardiac group the tendencies were the same, but the magnitude of the changes was greater when they occurred. Variations in heart rate were not greatly different in the two groups. The changes in cardiac output were grouped evenly around the zero point. The range of variation in both groups fell between −15 per cent and +14 per cent, which is the range of variation expected by this method.

## RESULTS

A. *Subjects With Essentially Normal Circulation.*—

1. *The Effect of Quinidine on Arterial and Right Ventricular Blood Pressures (Table II)*: Of the eight subjects studied, four (R. K., F. N., H. W., and J. S.) showed a significant fall in systolic, diastolic, and mean arterial pressures. The smallest falls were, in millimeters of mercury, −18 systolic and −12 diastolic, and the greatest falls were −64 systolic and −33 diastolic. The right ventricular pressures were recorded in only two of these four patients and showed no change. In addition, one subject (M. R., Table II) demonstrated a significant rise (systolic +37, diastolic +16 mm. Hg) in arterial blood pressures followed by an equally large fall (systolic −28, diastolic −9 mm. Hg). There was no change in the right ventricular pressures. Three subjects showed no change in arterial pressures. Of these, two had right ventricular pressures recorded and neither showed any change. The fall in arterial blood pressure was first noted at one to one and one-half hours and reached its maximum two hours after the drug was administered. In this acute experiment the duration of the fall in blood pressure could not be determined as the majority of the patients were only studied from two to two and one-half hours after the administration of the drug.

Comparison with the control data in Table I shows that the arterial pressure fall in these four of eight subjects was much beyond the normal range of variation and was presumably a quinidine effect.

2. *The Effect of Quinidine on Heart Rate (Table II)*: Seven subjects were followed for changes in heart rates. Five showed no change, and two (O. S. and J. S.) showed an increase in rate. One (O. S.) of these two had no change in blood pressure; the increase in rate of the other (J. S.), however, occurred at the time of the fall in arterial blood pressure.

3. *The Effect of Quinidine on Cardiac Output (Table III)*: Cardiac output was determined in five of the eight normal subjects and no change was noted. Three of these five subjects had significant falls in arterial blood pressure and two had no change.

4. *The Effect of Quinidine on Peripheral Resistance (Table III)*: Since one of the two variables used for the calculation of peripheral vascular resistance, namely, the cardiac output, was found not to change significantly in the normal subjects, it is only in the cases where the mean arterial pressure decreased that the vascular resistance was reduced. There were three such subjects (F. N., M. R., and H. W.) out of the five where the computation could be made. The peripheral resistance in these subjects was reduced, respectively, by 33 per cent,

TABLE II. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN EIGHT SUBJECTS WITH ESSENTIALLY NORMAL CIRCULATION

| CASE | TIME (MIN.) | HEART RATE (PER MIN.) | BRACHIAL ARTERY (MM. HG) | | | RIGHT VENTRICLE (MM. HG) | |
|---|---|---|---|---|---|---|---|
| | | | SYSTOLIC | DIASTOLIC | MEAN | SYSTOLIC | DIASTOLIC |
| H. C., male, 39 years; B. S. A. 1.82; infectious hepatitis, subsiding | Control | 80, 75, 75, 80 | 144 | 82 | 104 | — | — |
| | | | 150 | 85 | 110 | — | — |
| | 30* | 90 | 161 | 93 | 123 | — | — |
| | 60 | 90 | 137 | 77 | 100 | — | — |
| | 90 | 90 | 138 | 79 | 102 | — | — |
| | 125 | 80 | 140 | 80 | 105 | — | — |
| F. N., male, 46 years; B. S. A. 1.76; bronchiectasis | Control | 68, 75 | 110 | 68 | 87 | 27 | 6 |
| | 29* | 62 | 115 | 70 | 91 | 25 | 6 |
| | 44 | 71 | 102 | 63 | 80 | — | — |
| | 67 | 83 | 94 | 58 | 72 | 28 | 6 |
| | 87 | 78 | 88 | 55 | 69 | — | — |
| | 117 | 78 | 87 | 53 | 67 | 24 | 5 |
| | 127 | 71 | 85 | 52 | 66 | — | — |
| M. R., male, 49 years; B. S. A. 1.70; postpneumonia | Control | 62, 65, 65 | 104 | 50 | 80 | 23 | 5 |
| | | | 125 | 73 | 93 | | |
| | 28* | 68 | 136 | 78 | 102 | 20 | 3 |
| | 53 | 62 | 147 | 80 | 107 | — | — |
| | 63 | 65 | 152 | 82 | 108 | 23 | 6 |
| | 88 | 75 | 113 | 69 | 86 | 18 | 4 |
| | 133 | 68 | 87 | 57 | 70 | 16 | 2 |
| | 148 | 71 | 92 | 63 | 77 | — | — |
| W. M.,† male, 46 years; B. S. A. 1.74; central nervous system syphilis and hemiparesis | Control | 85, 83, 78 | 155 | 86 | 115 | — | — |
| | 12* | 83 | 156 | 87 | 118 | 25 | 6 |
| | 30 | 75 | 150 | 86 | 114 | 28 | 5 |
| | 71 | 85 | 149 | 84 | 109 | 22 | 5 |
| | 97 | 85 | 153 | 88 | 114 | — | — |
| | 120 | 90 | 153 | 88 | 114 | — | — |
| H. W., male, 44 years; B. S. A. 1.71; polyneuritic syndrome | Control | 83, 88, 88 | 134 | 85 | 107 | — | — |
| | | | 145 | 90 | 113 | — | — |
| | 24* | 88 | 139 | 86 | 109 | — | — |
| | 54 | 88 | 130 | 85 | 105 | — | — |
| | 89 | 88 | 76 | 55 | 59 | — | — |
| | 124 | 83 | 92 | 66 | 79 | — | — |
| R. K., male, 49 years; B. S. A. 1.67; gonococcal arthritis, subsiding | Control | 75, 75, 75 | 112 | 66 | 85 | 26 | 4 |
| | | | 118 | 68 | 89 | | |
| | 30* | 75 | 119 | 73 | 93 | 26 | 3 |
| | 73 | | 90 | 50 | | | |
| J. S., male, 53 years; B. S. A. 1.69; pulmonary fibrosis and emphysema, bronchiectasis | Control | 83, 115, 115 | 93 | 66 | 79 | 30 | 1 |
| | | | 89 | 64 | 75 | | |
| | 25* | 107 | 104 | 71 | 86 | — | — |
| | 43 | 107 | 92 | 66 | 78 | 26 | 1 |
| | 55 | 115 | 96 | 69 | 80 | 27 | 2 |
| | 95 | 125 | 74 | 52 | 62 | — | — |
| | 123 | 125 | 73 | 53 | 63 | — | — |

TABLE II. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN EIGHT SUBJECTS WITH ESSENTIALLY NORMAL CIRCULATION—(CONTINUED)

| CASE | TIME (MIN.) | HEART RATE (PER MIN.) | BRACHIAL ARTERY (MM. HG) | | | RIGHT VENTRICLE (MM. HG) | |
|---|---|---|---|---|---|---|---|
| | | | SYSTOLIC | DIASTOLIC | MEAN | SYSTOLIC | DIASTOLIC |
| O. S., male, 33 years; B. S. A. 1.77; chronic alcoholism, postpneumonia | Control | 75, 78, 71 | 116<br>117 | 69<br>65 | 91<br>89 | 28 | 3 |
| | 27* | 83 | 114 | 65 | 88 | 23 | 5 |
| | 45 | 71 | 119 | 70 | 90 | 23 | 5 |
| | 103 | 107 | 110 | 68 | 91 | 28 | 6 |
| | 125 | 107 | 114 | 68 | 92 | 27 | −1 |
| | 140 | 120 | 111 | 68 | 91 | — | — |

*Time after quinidine administration.
†Femoral artery pressures during entire study.
B.S.A. = body surface area in square meters.

TABLE III. THE EFFECT OF QUINIDINE ON CARDIAC OUTPUT, PERIPHERAL RESISTANCE, AND BLOOD VOLUME IN FIVE SUBJECTS WITH ESSENTIALLY NORMAL CIRCULATION

| CASE | TIME (MIN.) | CARDIAC INDEX (1/MIN./SQ. M.) | OXYGEN COMSUMPTION (C.C./MIN.) | A-V $O_2$ DIFF. (VOL. %) | PERIPHERAL RESISTANCE (DYNES, SEC., $CM^{-5}$) | BLOOD VOLUME | |
|---|---|---|---|---|---|---|---|
| | | | | | | TOTAL (C.C.) | PLASMA (C.C.) |
| H. C., male, 39 years; B. S. A. 1.82; infectious hepatitis, subsiding | Control | 5.13 | 281 | 3.0 | 894 | 6200 | 3710 |
| | 60* | 4.43 | 273 | 3.4 | 995 | | |
| | 125 | 4.76 | 277† | 3.2 | 945 | | |
| | 145 | 4.92 | 277† | 3.1 | — | 5850 | 3510 |
| F. N., male, 46 years; B. S. A. 1.76; bronchiectasis | Control | 2.91 | 266 | 5.2 | 1355 | — | — |
| | 117* | 3.28 | 249 | 4.3 | 907 | — | — |
| M. R., male, 49 years; B. S. A. 1.70; postpneumonia | Control | 2.71 | 244 | 5.3 | 1500 | 3640 | 1950 |
| | 88* | 2.49 | 227 | 5.3 | 1630 | | |
| | 125 | 2.95 | 261 | 5.2 | 1100 | 4120 | 2190 |
| W. M., male, 46 years; B. S. A. 1.74; central nervous system syphilis and hemiparesis | Control | 3.66 | 204 | 3.2 | 1393 | — | — |
| | 71* | 3.50 | 210 | 3.5 | 1440 | — | — |
| | 120 | 3.11 | 195 | 3.6 | 1665 | — | — |
| H. W., male, 44 years; B. S. A. 1.71; polyneuritic syndrome | Control | 3.19 | 262 | 4.8 | 1620 | — | — |
| | 54* | 3.42 | 275 | 4.7 | 1440 | — | — |
| | 124 | 2.83 | 242 | 5.0 | 1308 | — | — |

*Time after quinidine administration.
†Assumed oxygen consumption (average of values obtained in first and second cardiac outputs).
B. S. A. = body surface area in square meters.

27 per cent, and 19 per cent. In the two other subjects (H. C. and W. M.) with only small changes in cardiac output and mean blood pressure, the peripheral resistance increased by 11 per cent and 20 per cent, respectively. Since the accepted variation in cardiac output is plus or minus 15 per cent for this study, it is clear that in the expression of peripheral resistance, as here calculated, a fluctuation of the same magnitude can be expected if the mean arterial pressure does not change. Hence, in the two subjects with unchanged blood pressure, these variations in peripheral resistance probably represent fluctuations within the expected range. On the other hand, in the subject H. W. a fall in peripheral resistance of 19 per cent is probably a true expression of a change in the peripheral arteriolar bed, as it was associated with a fall in blood pressure.

5. *The Effect of Quinidine on Blood Volume* (*Table III*): In one (H. C.) of the two patients studied, total blood volume was reduced by 5 per cent after quinidine, and in the other subject (M. R.), it was increased by 13 per cent. These changes are probably not significant.

*Discussion of Changes Produced by Quinidine in Normal Subjects* (*Tables II and III*).—The only significant change in the hemodynamics of normal circulation was a fall in arterial blood pressure in one-half the cases studied. Subject M. R. had a rise in blood pressure during the early phase of the investigative period, and from this higher level of pressure there developed a marked fall which persisted for one hour. In three subjects a fall in peripheral resistance was associated with the fall in blood pressure, suggesting an action of quinidine on the peripheral vascular bed. Right ventricular pressures were not altered by quinidine.

There were no significant changes in heart rate, cardiac output, and blood volume.

B. *Patients With Cardiovascular Disease.*—

1. *The Effect of Quinidine on Arterial and Right Ventricular Blood Pressures* (*Table IV*): The data presented in Table I were also used as a guide for the interpretation of significant changes in blood pressures, heart rate, and cardiac output in these cases of cardiac disease.

*Group A*: One (R. C.) of the two patients showed a fall in arterial systolic, diastolic, and mean pressures, while the other (M. I.) showed no change. Right ventricular pressures were recorded in both instances and were not altered.

*Group B*: The one patient (P. B.) in this group showed a fall in arterial systolic, diastolic, and mean pressures. The right ventricular systolic pressure fell; the diastolic pressure did not vary.

*Group C*: This patient (S. H.) showed one of the most marked falls in arterial blood pressures, 65 mm. Hg systolic and 32 mm. Hg diastolic. Only one other patient (H. I.) had a larger fall in diastolic pressure, 46 mm. of mercury. A concomitant fall occurred in the right ventricular systolic pressure; the right ventricular diastolic pressure did not change.

TABLE IV. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE

| CASE | TIME (MIN.) | HEART RATE (PER MIN.) | BRACHIAL ARTERY (MM. HG) | | | RIGHT VENTRICLE (MM. HG) | |
|---|---|---|---|---|---|---|---|
| | | | SYSTOLIC | DIASTOLIC | MEAN | SYSTOLIC | DIASTOLIC |
| *Group A. Normal Cardiac Output; Elevated Right Ventricular Pressures* | | | | | | | |
| M. I., female, 23 years; B. S. A. 1.71; interventricular septal defect; NSR, IA | Control | 60, 62, 71, 68 | 114 | 59 | 74 | 21 | 8 |
| | | | 103 | 62 | 72 | | |
| | | | 103 | 63 | 70 | | |
| | | | (By sphygmomanometer) | | | | |
| | 30* | 80 | 110 | 70 | — | — | — |
| | 65 | 65 | 112 | 70 | — | 18 | 8 |
| | 85 | 85 | 118 | 72 | — | 19 | 7 |
| | 112 | 70 | 118 | 70 | — | 20 | 8 |
| R. C., male, 14 years; B. S. A. 1.66; RHD, EH, MS, MI, AI, SA; incomplete A-V block, IA | Control | 70, 68 | 130 | 65 | 92 | 38 | 5 |
| | 26* | 83 | 137 | 75 | 103 | — | — |
| | 60 | 70 | 144 | 69 | 100 | 40 | 10 |
| | 110 | 93 | 68 | 42 | 56 | — | — |
| | 125 | 100 | 82 | 45 | 60 | 41 | 3 |
| *Group B. High Cardiac Output; Elevated Right Ventricular Pressures* | | | | | | | |
| P. B., male, 55 years; B. S. A. 1.72; Unk. HD, EH, NSR, IA; ? cor pulmonale | Control | 115, 100, 100, 100 | 146 | 85 | 112 | 36 | 5 |
| | | | 142 | 82 | 108 | — | — |
| | 57* | 100 | 106 | 66 | 85 | 25 | 3 |
| | 119 | 88 | 125 | 73 | 96 | 21 | 3 |
| *Group C. Low Cardiac Output; Elevated Right Ventricular Pressures; No Digitalis* | | | | | | | |
| S. H.,† male, 57 years; B. S. A. 1.50; HCVD, ASHD, EH, CS, MF, NSR, CI, PND, LBBB, IIIC | Control | 65, 75, 71 | 197 | 108 | 135 | 33 | 7 |
| | 30* | 70, 80 | 139 | 76 | 100 | 25 | 3 |
| | 42 | 80 | 139 | 80 | 102 | 21 | 3 |
| | 82 | 83 | 132 | 76 | 98 | 19 | 4 |
| | 94 | 95 | 148 | 83 | 112 | — | — |
| | 107 | 100 | 157 | 86 | 111 | — | — |
| *Group D. Low or Normal Cardiac Output; Elevated Right Ventricular Pressures; Digitalized* | | | | | | | |
| H. I., male, 51 years; B. S. A. 1 70; HCVD, EH, NSR, CI, IIIC; arteriolar nephrosclerosis | Control | 93, 88, 88 | 218 | 125 | 158 | 60 | 9 |
| | | | 222 | 130 | 162 | | |
| | 10* | 88 | 218 | 122 | 156 | 56 | 5 |
| | 35 | 83 | 218 | 125 | 158 | — | — |
| | 40 | 83 | 217 | 125 | 154 | 51 | 6 |
| | 60 | 88 | 218 | 125 | 151 | 43 | 9 |
| | 95 | 86 | 219 | 117 | 156 | 56 | 8 |
| | 110 | 86 | 216 | 114 | 152 | 56 | 8 |
| | 127 | 86 | 230 | 117 | 154 | 41 | 11 |
| | 145 | 80 | 187 | 96 | 129 | — | — |
| | 155 | 78 | 176 | 90 | 118 | 39 | 7 |
| | 160 | 80 | 161 | 82 | 110 | — | — |

*Continued on next page. All footnotes appear at end of table.*

TABLE IV. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE—(CONTINUED)

| CASE | TIME (MIN.) | HEART RATE (PER MIN.) | BRACHIAL ARTERY (MM. HG) | | | RIGHT VENTRICLE (MM. HG) | |
|---|---|---|---|---|---|---|---|
| | | | SYSTOLIC | DIASTOLIC | MEAN | SYSTOLIC | DIASTOLIC |
| H. C., male, 45 years; B. S. A. 1.85; coarctation of the aorta; EH, NSR, PND, CI, IIIC | Control | 75, 71, 71, 68 | 225 | 108 | 145 | 65 | 12 |
| | | | 118‡ | 90‡ | 103‡ | | |
| | | | 224 | 120 | 151 | | |
| | 35* | 71 | 234 | 123 | 160 | 67 | 6 |
| | 58 | 68 | 234 | 122 | 157 | 65 | — |
| | 86 | 71 | 234 | 123 | 156 | 65 | 9 |
| | 115 | 75 | 226 | 115 | 149 | 41 | 3 |
| | 133 | 75 | 222 | 120 | 153 | 36 | 2 |
| | | | 110‡ | 81‡ | 95‡ | | |
| | 138 | 71 | 215 | 107 | 138 | — | — |
| | | | 108‡ | 83‡ | 94‡ | | |
| | 148 | 68 | 219 | 110 | 144 | 36 | 3 |
| | 156 | 68 | 216 | 106 | 138 | — | — |
| J. L., male, 63 years; B. S. A. 1.43; RHD, EH, MS, MI, AI, NSR, CI, IIIC | Control | 68, 68, 71, 71 | 150 | 79 | 109 | 38 | 2 |
| | | | 147 | 77 | 106 | | |
| | 29* | 78 | 134 | 70 | 97 | — | — |
| | 54 | 71 | 109 | 56 | 73 | — | — |
| | 62 | 75 | 101 | 55 | 74 | — | — |
| | 92 | 75 | 99 | 53 | 72 | — | — |
| | 97 | 75 | 102 | 56 | 75 | 26 | −1 |
| | 132 | 75 | 109 | 59 | 82 | 25 | 2 |
| T. C., male, 49 years; B. S. A. 1.62; cor pulmonale; EH, NSR, CI, IIIC; Pulm. F and E | Control | 115, 107, 115 | 115 | 74 | 89 | 110 | 7 |
| | 55* | 115 | 85 | 49 | 62 | 93 | 8 |
| | 73 | 115 | — | — | — | 100 | 5 |
| | 88 | 115 | 101 | 63 | 79 | 96 | 8 |
| | 110 | 115 | 114 | 65 | 84 | 95 | 10 |
| | 130 | 115 | — | — | — | 107 | 9 |
| *Group E. Low or Low Normal Cardiac Output; Normal Right Ventricular Pressures; Digitalized* | | | | | | | |
| W. W., male, 46 years; B. S. A. 1.92; ASHD, EH, CS, MF, AF, IIB | Control | 80, 60, 90, 80 | 110 | 75 | 92 | 28 | 2 |
| | | | 108 | 75 | 89 | | |
| | 10* | 95 | 134 | 97 | 111 | 27 | 1 |
| | 17 | 95 | 145 | 99 | 115 | 28 | 2 |
| | 33 | 100 | 126 | 86 | 103 | 26 | 1 |
| | 90 | 110 | 104 | 75 | 84 | 21 | 0 |
| | 120 | 100 | 112 | 77 | 83 | 22 | 1 |
| D. P.,† male, 60 years; B. S. A. 1.91; ASHD, EH, CS, MF; old myocardial infarct; NSR, IIB | Control | 83, 75, 75, 75 | 115 | 68 | 91 | 28 | 4 |
| | | | 122 | 72 | 94 | | |
| | | | 118 | 68 | 90 | | |
| | 27* | 71 | 113 | 73 | 89 | 23 | 0 |
| | 54 | 75 | 128 | 63 | 97 | 25 | 1 |
| | 85 | 83 | 120 | 73 | 94 | — | — |
| | 117 | 88 | 113 | 71 | 94 | 29 | 0 |
| | 127 | 88 | 114 | 68 | 87 | — | — |
| | 142 | 88 | 120 | 73 | 96 | 31 | 4 |
| | 162 | 83 | 114 | 65 | 87 | — | — |

*Continued on next page. All footnotes appear at end of table.*

TABLE IV. THE EFFECT OF QUINIDINE ON HEART RATE AND BLOOD PRESSURES IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE—(CONTINUED)

| CASE | TIME (MIN.) | HEART RATE (PER MIN.) | BRACHIAL ARTERY (MM. HG) | | | RIGHT VENTRICLE (MM. HG) | |
|---|---|---|---|---|---|---|---|
| | | | SYSTOLIC | DIASTOLIC | MEAN | SYSTOLIC | DIASTOLIC |
| J. W., male, 64 years; B. S. A. 1.75; ASHD, ?HCVD, EH, CS, MF, NSR, IIB | Control | 71, 68, 65 | 110 | 61 | 82 | 27 | 4 |
| | | | 107 | 62 | 82 | | |
| | 60* | 68 | 130 | 67 | 93 | 34 | 4 |
| | 80 | 75 | 120 | 67 | 89 | — | — |
| | 91 | 71 | 128 | 73 | 98 | — | — |
| | 113 | 75 | 118 | 67 | 89 | 31 | 6 |
| | 128 | 71 | 125 | 67 | 89 | — | — |
| C. L., male, 57 years; B. S. A. 1.72; Unk. HD, EH, AF, IIB | Control | 70, 70, 80, 70 | 99 | 52 | 68 | 22 | 4 |
| | | | 115 | 55 | 80 | | |
| | | | 112 | 54 | 77 | | |
| | 50* | 80 | 117 | 58 | 84 | 23 | 4 |
| | 90 | 90 | 81 | 48 | 50 | 18 | 1 |
| | 115 | 90, 80 | 93 | 53 | 67 | 22 | 5 |
| | 120 | 90 | 87 | 51 | 66 | — | — |

*Time after quinidine administration.
†Femoral artery pressures during entire study.
‡Femoral artery pressures.

B. S. A. Body surface area in square meters.
ASHD Arteriosclerotic heart disease.
HCVD Hypertensive cardiovascular disease.
RHD Rheumatic heart disease.
Unk. HD Heart disease of unknown type.

AF Auricular fibrillation.
CI Cardiac insufficiency.
PND Paroxysmal nocturnal dyspnea.
NSR Normal sinus rhythm.
SA Sinus arrhythmia.
LBBB Left bundle branch block.

AI Aortic insufficiency.
CS Coronary sclerosis.
EH Enlarged heart.
MI Mitral insufficiency.
MF Myocardial fibrosis.
MS Mitral stenosis.

Pulm. F and E Pulmonary fibrosis and emphysema.

*Group D*: All four patients in this group demonstrated a fall in arterial systolic, diastolic, and mean pressures, although Patient H. C. with coarctation of the aorta showed only a minimal fall in both brachial and femoral artery pressures. In every instance the right ventricular systolic pressure fell, but the right ventricular diastolic pressure of only one patient (H. C.) was decreased. This patient also had the greatest fall in right ventricular systolic pressure (29 mm. of mercury).

*Group E*: One patient (C. L.) showed a fall, two (W. W. and J. W.), a rise, and one (D. P.), no change in arterial blood pressures. None of the four had any alterations in right ventricular pressures.

Of the twelve cardiac patients, irrespective of groups, eight showed a fall in arterial pressures, two showed no change, and two, a rise. Six of the eight also showed a fall in right ventricular systolic pressure; in only one of these did the

diastolic fall. Six patients showed no significant variations from the control values in the right ventricular pressures.

The fall in both arterial and right ventricular pressures was first seen as early as thirty minutes and as late as 145 minutes after ingestion of the drug. The fall in right ventricular pressures was associated in every instance with a fall in peripheral artery pressure. The rise in arterial blood pressure was noted as early as ten minutes after the administration of quinidine.

2. *The Effect of Quinidine on Heart Rate* (*Table IV*): The heart rate rose in five of the twelve patients (M. I., R. C., S. H., W. W., and C. L.), while in two patients (P. B. and H. I.) it fell, and in five (T. C., H. C., J. L., D. P., and J. W.), did not vary significantly. Three (H. C., J. L., and T. C.) of the eight patients who had falls in arterial blood pressure showed no change in heart rate, three (S. H., R. C., and C. L.) showed a rise, and two (P. B. and H. I.), a fall. One of the two subjects (D. P.) who had no change in arterial blood pressure had no significant alteration in heart rate, while the heart rate of the other (M. I.) rose. One (W. W.) of the patients with a rise in arterial blood pressure also had a rise in heart rate, while the heart rate of the other (J. W.) did not vary.

3. *The Effect of Quinidine on Cardiac Output* (*Table V*):

*Group A*: The two patients in this group demonstrated no change in cardiac output. A fall in arterial blood pressure was seen in one (R. C.).

*Group B*: In this one patient a fall in arterial and right ventricular pressures was accompanied by a fall of 19.2 per cent in cardiac output without change in heart rate.

*Group C*: The patient in this group had an increase of 18 per cent in cardiac output occurring simultaneously with the maximum fall in arterial and right ventricular pressures. At that time his heart rate had not changed significantly.

*Group D*: Three patients in this group showed a rise in cardiac output (20.7 37.1, and 30.4 per cent) associated with falls in arterial and ventricular blood pressures. The one patient (H. I.) who showed no significant alteration in cardiac output unfortunately did not have a cardiac output determination at the time of his fall in arterial blood pressure. None of these patients showed any real variation in heart rate.

*Group E*: The cardiac output of two of these patients (J. W. and C. L.) rose considerably (40.4 and 62.3 per cent, respectively), while the other two patients showed no change. In one patient (C. L.) the increase in cardiac output was associated with a fall in arterial blood pressure, no change in right ventricular pressures, and a slight rise in heart rate. The other patient (J. W.) had a slight rise in arterial blood pressure but no change in heart rate.

4. *The Effect of Quinidine on Peripheral Resistance* (*Table V*):

*Group A*: Only one (R. C.) of the two patients was examined for changes in peripheral resistance. Simultaneously with a fall in arterial blood pressure

the peripheral resistance fell 36 per cent and there was no change in cardiac output. Heart rate increased at the time of maximum hemodynamic changes.

*Group B*: A significant fall in blood pressure and in cardiac output occurred in Patient P. B. without any real change in peripheral resistance. The heart rate fell slightly.

*Group C*: Patient S. H. demonstrated a fall in arterial and right heart pressures associated with a rise in cardiac output and a 40 per cent fall in peripheral resistance. The heart rate did not increase until some time after the major changes in the circulation had taken place.

*Group D*: All four patients in this group followed the same pattern of response to quinidine. In each patient there was a considerable fall in arterial blood pressure, with the exception of H. C. in whom coarctation of the aorta may have added a barrier to arterial blood pressure change. In all four patients the right ventricular pressures fell quite markedly. In the case of Patient H. C., this fall was very large. In the three subjects (H. C., J. L., and T. C.) in whom cardiac output was measured at the time of the blood pressure fall, all three clearly showed a marked rise in cardiac output and a fall in peripheral resistance of −25, −50, and −35.7 per cent, respectively. The smallest fall in peripheral resistance was in the case of coarctation.

*Group E*: The patient (C. L.) whose arterial blood pressure fell showed a rise in cardiac output, no right ventricular pressure change, and a slight increase in heart rate. It was of interest in this case that the fall in peripheral resistance and the rise in cardiac output appeared some time before the fall in arterial blood pressure. Patient J. W. had a rise in cardiac output and a fall in peripheral resistance, but a rise in arterial blood pressure. The other two patients (W. W. and D. P.) showed no change in peripheral resistance.

5. *The Effect of Quinidine on Blood Volume* (*Table V*): Ten patients were studied for changes in total blood and plasma volume. Five patients showed an increase (6.7 to 13.9 per cent) in total blood volume, two, a decrease of 9 and 11 per cent, and four showed no change.

*Discussion of Circulatory Changes Produced by Quinidine in Patients With Cardiovascular Disease*: While there was no uniform effect of quinidine on the circulation in patients with cardiovascular disease, there occurred in most a significant lowering of arterial blood pressure. Eight of the twelve patients showed this change. This corresponds with the similar effect in four of the eight normal subjects.

In the normal subjects, as has been indicated, the fact that the arterial blood pressures tended to fall, while there was no change in right ventricular pressures or in cardiac output, suggests that this action of quinidine was largely or wholly peripheral: a vasodilatation of systemic arterioles.

In the patients with cardiovascular disease the total effects of quinidine were more extensive, though they varied in the different physiologic groups.

The two patients in Group A whose hearts were clinically not decompensated but showed some right ventricular systolic or diastolic hypertension

TABLE V. THE EFFECT OF QUINIDINE ON CARDIAC OUTPUT, PERIPHERAL RESISTANCE, AND BLOOD VOLUME IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE

| CASE | TIME (MIN.) | CARDIAC INDEX (L/MIN./SQ. M.) | OXYGEN CONSUMPTION (C.C./MIN.) | A-V $O_2$ DIFF. (VOL. %) | PERIPHERAL RESISTANCE (DYNES, SEC., CM$^{-5}$) | BLOOD VOLUME | |
|---|---|---|---|---|---|---|---|
| | | | | | | TOTAL (C.C.) | PLASMA (C.C.) |
| *Group A. Normal Cardiac Output; Elevated Right Ventricular Pressures* | | | | | | | |
| M. I., female, 23 years; B. S. A. 1.71; interventricular septal defect; NSR, IA | Control | 2.60‡ | 236 | 5.3 | — | — | — |
| | 65* | 2.47 | 207 | 4.9 | — | — | — |
| | 112 | 2.31 | 213 | 5.4 | — | — | — |
| R. C., male, 14 years; B. S. A. 1.66; RHD, EH, MS, MI, AI, SA; incomplete A-V block, IA | Control | 3.02 | 145 | 3.1 | 1470 | 4320 | 2700 |
| | 125* | 3.10 | 170 | 3.3 | 930 | 4825 | 3020 |
| *Group B. High Cardiac Output; Elevated Right Ventricular Pressures* | | | | | | | |
| P. B., male, 55 years; B.S.A. 1.72; Unk. HD, EH, NSR, IA; ? cor pulmonale | Control | 4.75 | 286 | 3.5 | 1080 | 5725 | 3490 |
| | 57* | 3.83 | 264 | 4.1 | 1033 | — | — |
| | 119 | 4.00 | 275† | 4.0 | 1110 | — | — |
| | 149 | — | — | — | — | 5720 | 3200 |
| *Group C. Low Cardiac Output; Elevated Right Ventricular Pressures; No Digitalis* | | | | | | | |
| S. H., male, 57 years; B.S.A. 1.50; HCVD, ASHD, EH, CS, MF, NSR, CI, PND, LBBB, IIIC | Control | 2.03 | 174 | 5.7 | 3530 | 4360 | 2640 |
| | 42* | 1.86 | 139 | 5.0 | 2910 | — | — |
| | 82 | 2.40 | 187 | 5.2 | 2110 | — | — |
| | 107 | — | — | — | — | 4650 | 2800 |
| *Group D. Low or Normal Cardiac Output; Elevated Right Ventricular Pressures; Digitalized* | | | | | | | |
| H. I., male, 51 years; B.S.A. 1.70; HCVD, EH, NSR, CI, IIIC; arteriolar nephrosclerosis | Control | 2.77 | 283 | 6.0 | 2630 | 5460 | 3050 |
| | 60* | 2.64 | 269 | 6.0 | 2600 | — | — |
| | 127 | 2.84 | 290 | 6.0 | 2480 | 6220 | 3820 |
| H. C., male, 45 years; B.S.A. 1.85; coarctation of the aorta; EH, NSR, PND, CI, IIIC | Control | 2.76 | 250 | 4.9 | 2280<br>1570§ | 6000 | 3845 |
| | 58* | 2.71 | 280 | 5.6 | 2460 | — | — |
| | 133 | 3.49 | 309 | 4.8 | 1700 | — | — |
| | 156 | — | — | — | 1165§<br>— | 5330 | 3465 |

TABLE V. THE EFFECT OF QUINIDINE ON CARDIAC OUTPUT, PERIPHERAL RESISTANCE, AND BLOOD VOLUME IN TWELVE PATIENTS WITH CARDIOVASCULAR DISEASE—(CONTINUED)

| CASE | TIME (MIN.) | CARDIAC INDEX (L/MIN./SQ. M.) | OXYGEN CONSUMPTION (C.C./MIN.) | A V $O_2$ DIFF. (VOL. %) | PERIPHERAL RESISTANCE (DYNES, SEC., $CM^{-5}$) | BLOOD VOLUME | |
|---|---|---|---|---|---|---|---|
| | | | | | | TOTAL (C.C.) | PLASMA (C.C.) |
| J. L., male, 63 years; B.S.A. 1.43; RHD, EH, MS, MI, AI, NSR, CI, IIIC | Control | 2.05 | 173 | 5.9 | 2950 | 3995 | 2145 |
| | 62* | 2.81 | 181 | 4.5 | 1470 | —— | —— |
| | 132 | 2.45 | 182 | 5.2 | 1880 | 4445 | 2440 |
| T. C., male, 49 years; B.S.A. 1.62; cor pulmonale; EH, NSR, CI, IIIC; Pulm. F and E | Control | 3.18 | 345 | 6.7 | 1380 | 6740 | 2930 |
| | 55* | 3.43 | 317 | 5.7 | 887 | —— | —— |
| | 110 | 4.15 | 316 | 4.7 | 1000 | 6130 | 2760 |
| *Group E. Low or Low Normal Cardiac Output; Normal Right Ventricular Pressures; Digitalized* | | | | | | | |
| W. W., male, 46 years; B.S.A. 1.92; ASHD, EH, CS, MF, AF, IIB | Control | 2.23 | 270 | 6.3 | 1705 | 6780 | 3030 |
| | 57* | 2.13 | 274 | 6.7 | —— | —— | —— |
| | 120 | 2.32 | 311 | 7.0 | 1482 | 7270 | 3270 |
| D. P., male, 60 years; B.S.A. 1.91; ASHD, EH, CS, MF; old myocardial infarct; NSR, IIB | Control | 1.59 | 213 | 7.0 | 2360 | 4970 | 1655 |
| | 54* | 1.65 | 205 | 6.5 | 2450 | —— | —— |
| | 162 | 1.44 | 217 | 7.9 | 2530 | 4810 | 1595 |
| J. W., male, 64 years; B.S.A. 1.75; ASHD, ?HCVD, EH, CS, MF, NSR, IIB | Control | 2.77 | 252 | 5.2 | 1400 | 7250 | 4135 |
| | 60* | 3.43 | 258 | 4.3 | 1285 | —— | —— |
| | 113 | 3.89 | 279 | 4.1 | 1035 | 6960 | 3895 |
| C. L., male, 57 years; B.S.A. 1.72; Unk. HD, EH, AF, IIB | Control | 1.68 | 275 | 9.5 | 1970 | —— | —— |
| | 50* | 2.72 | 296 | 6.3 | 1008 | —— | —— |
| | 115 | 1.82 | 206 | 6.6 | 1690 | 8210 | 5000 |

*Time after quinidine administration.

†Assumed oxygen consumption (average of values obtained in first and second cardiac outputs).

‡Aortic flow and blood returning to the right auricle. Pulmonary flow, measured once, was somewhat larger because of the presence of the interventricular septal defect.

§Calculated on basis of femoral artery mean pressures.

B. S. A. = body surface area in square meters.

ASHD Arteriosclerotic heart disease.
HCVD Hypertensive cardiovascular disease.
RHD Rheumatic heart disease.
Unk. HD Heart disease of unknown type.

AI Aortic insufficiency.
CS Coronary sclerosis.
EH Enlarged heart.
MI Mitral insufficiency.
MF Myocardial fibrosis.
MS Mitral stenosis.

AF Auricular fibrillation.
CI Cardiac insufficiency.
PND Paroxysmal nocturnal dyspnea.
NSR Normal sinus rhythm.
SA Sinus arrhythmia.
LBBB Left bundle branch block.

Pulm. F and E Pulmonary fibrosis and emphysema.

behaved like the normal subjects, one patient showing a fall in arterial pressure and the other not, but both having no change in right ventricular pressures nor in their (normal) values of cardiac output, as a result of quinidine. In the one patient showing a decreased arterial pressure, this effect was thus apparently a peripheral vasodilatation.

The patient in Group B with a high cardiac output and right-sided systolic hypertension, without clinical evidence of decompensation, showed a fall in arterial pressure, in the elevated right ventricular pressure, and in cardiac output, after quinidine. Presumably these pressure effects were chiefly due to vasodilatation. Some depressive action on the heart itself cannot be excluded. This was the only instance of this type of response.

Groups C and D, patients with initially low cardiac outputs, elevated right ventricular pressures, and, in addition, clinical signs of failure, showed significantly different reactions to quinidine from the patients whose cases have just been cited. Both the nondigitalized patient of Group C and the four digitalized patients of Group D had, after quinidine: (1) fall in arterial pressures, (2) fall in right ventricular systolic pressures, and (3) a considerable increase in cardiac output.

This series of events could be explained on the basis that the peripheral vasodilator effect of quinidine, in lowering arterial pressure, relieved the strain on the left heart, allowing it to empty more completely, with increased stroke volume; this, in turn, decreased pulmonary congestion and lowered right ventricular systolic pressure.

It is also possible, however, that quinidine may have produced the increase in cardiac output, in part, by a direct action on the heart in these cases.

There is some further evidence suggestive of a direct action of quinidine on the heart. Patient H. C., for example, had only a minimal fall in arterial pressure, but a large drop in right ventricular pressures and a large increase in cardiac output.

The results in Group E, while not very consistent, are also somewhat suggestive of a direct effect of quinidine on the heart. These individuals, as already noted, were patients with heart disease who had recovered clinical compensation at the time of study, and were classified II,B. In Patient C. L., with fall in arterial pressure and rise in cardiac output, the myocardial effect of quinidine is suggested by the fact that the increase in cardiac output took place before the arterial pressure fell. Patient J. W. had a 40 per cent increase in cardiac output, with a small rise in arterial blood pressure, again suggesting some myocardial action of the drug. In results as variable as those obtained in Group E, however, no definite conclusions can be drawn.

Variations in heart rate were not consistent in the cardiac cases and bore no constant relationship to any other circulatory changes. Blood volume changes were few and not correlated with other effects. It seems not unlikely that in the three hours of the study there may have been enough small fluctuations in body fluids to produce occasional irregular changes in blood volume.

In summary, the chief dynamic effect of a single dose of quinidine in subjects with normal circulations was a fall in arterial blood pressure which occurred in

about one-half of the cases, while in patients in clinical congestive heart failure, a fall in arterial blood pressure was usually combined with a drop in a previously elevated right ventricular systolic pressure and an increase in a previously low cardiac output.

It is hardly possible to apply these physiologic and pharmacologic data on the effects of a single dose of quinidine to the clinical use of the drug. It may be that the effects described are a part of its therapeutic action, especially the combined effects seen in the heart failure cases. If such is the case, the mechanism is as yet obscure. It seems fairly clear that quinidine action is fundamentally different from digitalis action, since the increased cardiac output is not associated with a fall in diastolic filling pressure as measured by right ventricular diastolic pressure.[32] Further work will be needed to decide this problem.

So far as the vasodilator action of quinidine is concerned, it is quite possible that in susceptible subjects this becomes an unfavorable effect. Routine examination of the blood pressure during quinidine therapy may settle this question.

C. *Electrocardiographic Changes Produced by Quinidine.*—Electrocardiographic changes were noted in all eight normal subjects and were of two types. In seven subjects there was a consistent decrease in amplitude of the T waves in standard Leads I and II, and occasionally in Lead III. In the eighth subject, T-wave changes were difficult to evaluate for technical reasons. The T-wave changes appeared as early as thirty minutes and as late as ninety-five minutes after quinidine. The second electrocardiographic abnormality produced was a prolongation of the Q-T interval to abnormal length in all eight normal subjects. This occurred as early as twenty-four minutes and as late as eighty-eight minutes after administration of the drug. In three subjects the Q-T interval change occurred before the T waves altered; in two the decrease in T-wave amplitude was noted first; and in two the changes occurred simultaneously. There was no change in P waves, P-R interval, or QRS duration.

Ten cardiac patients also showed electrocardiographic changes of the two types mentioned. The tracings in two patients with auricular fibrillation (W. W. and C. L.) could not be analyzed satisfactorily for either T-wave or Q-T interval changes. Eight of the ten cardiac patients had T-wave changes, which were noted as early as twenty-six minutes and as late as 160 minutes after quinidine. One patient's changes were equivocal and in the other patient's tracings the markedly prolonged Q-T interval made T-wave measurements difficult. The prolongation of the Q-T interval, noted in all ten cardiac patients, first appeared at thirty minutes in one patient and at 125 minutes in another. Three patients had T-wave changes appear before Q-T interval prolongation, while two had the changes appear in reverse order. In four patients the changes were simultaneous. In one patient (R. C.) with a prolonged P-R interval (0.24 second), the conduction time returned to normal (0.20 second) 115 minutes after the drug was given. Four of the cardiac patients developed a right bundle branch block pattern fifty-three to eighty-four minutes after administration of the drug. One patient with left bundle branch block and a QRS of 0.12 second was found to have a QRS of 0.14 second, 107 minutes after quinidine.

There was no significant alteration in the relationship of mechanical to electrical events[33] in the cardiac patients, with the exception of those in whom right bundle branch block appeared. In these patients the ventricular asynchronism typical of this abnormality became apparent.

The changes in the electrocardiograms of normal and cardiac subjects were interpreted as indicative of an effect of the drug on the myocardium. Since these changes appeared in all normal subjects and ten of the twelve cardiac patients, it can be stated that the drug reached the cardiac muscle. In the two patients with auricular fibrillation where no electrocardiographic effect of the drug could be noted, one (C. L.) had definite hemodynamic effects attributable to the drug and the other (W. W.) did not.

The electrocardiographic changes provide strong evidence that there is some central or myocardial action of quinidine.

D. *Ward Study.*—A supplementary study of the effect of quinidine on blood pressure alone was carried out on patients on the wards (Fig. 1). This

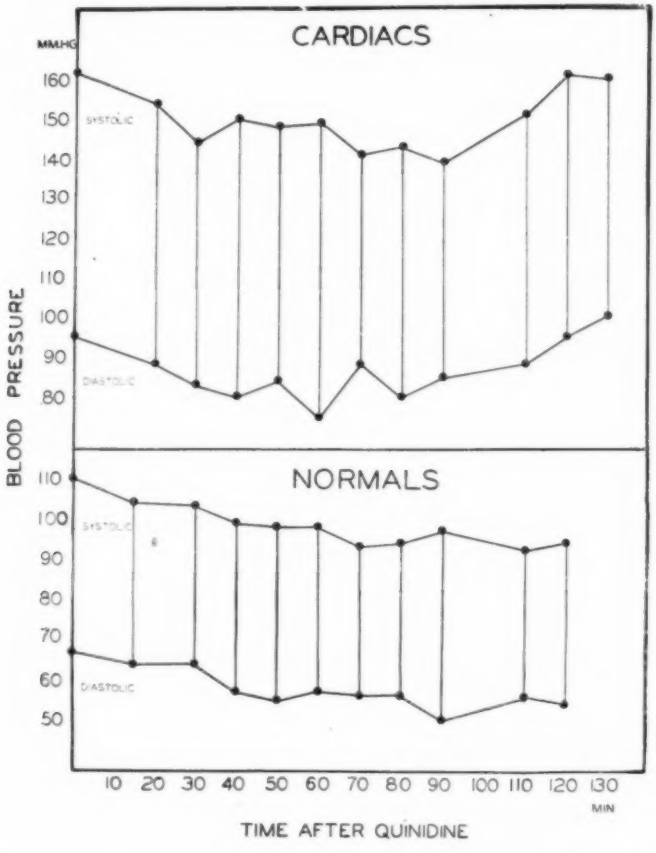


**Fig. 1.—The average effect of quinidine on arterial blood pressure in eleven cardiac patients and ten normal subjects.**

**Blood pressure was recorded by sphygmomanometer. Note the significant drop in both groups which averaged nearly 20 mm. Hg in both systolic and diastolic pressures.**

was done to confirm the unexpected blood pressure fall and to exclude the effects of sedation and the catheterization technique. Ten patients with essentially normal circulation and eleven patients with cardiovascular disease received 0.8 Gm. quinidine sulfate by mouth. These patients had been fasting and in bed for twelve hours and they had received no sedation for the twelve hours prior to the observation period. In the majority of patients three control blood pressure determinations, taken by sphygmomanometer, were obtained during the first half hour of the study. The range of variation for both systolic and diastolic pressures was computed from these control values and was found to be plus or minus 10 mm. Hg for both normal subjects and cardiac patients. In some instances wide fluctuations in diastolic pressures made any evaluation of a change impossible. Of the ten normal subjects, seven showed a definite fall in both systolic and diastolic pressures. The maximum changes were a fall of 61 mm. Hg systolic and 33 mm. Hg diastolic. Of the eleven cardiac patients, ten showed an unequivocal fall in both systolic and diastolic arterial blood pressures, and the greatest fall for each was 53 and 34 mm. Hg, respectively. One of these ten showed an early rise in blood pressure preceding the fall. One patient showed only a rise in blood pressure, but this patient was extremely restless throughout the study. In both normal subjects and patients with cardiovascular disease, the initial fall in blood pressure was recorded as early as fourteen minutes and as late as 123 minutes after administration of quinidine.

The average systolic and diastolic blood pressures of the ten normal subjects and eleven patients with cardiovascular disease are plotted in Fig. 1. Each point represents the average systolic or diastolic blood pressure of each group at the time indicated.

*Note on Side Effects of Quinidine.*—The dosage used (0.8 Gm.) produced gastrointestinal symptoms in only two (R. K. and A. S.) of the forty-one patients studied. These symptoms consisted of nausea, epigastric pain, and lower abdominal cramps and were associated with a fall in arterial blood pressure in both patients. No other side effects of the drug were encountered.

## SUMMARY AND CONCLUSIONS

The effect of 0.8 Gm. of oral quinidine sulfate on the heart and circulation was studied in forty-one subjects. In twenty patients an extensive investigation of the circulatory hemodynamics was carried out by means of the right heart catheterization technique. Clinical investigation of the blood pressure alone was undertaken in twenty-one subjects.

1. A fall in arterial blood pressure was found in twelve of the eighteen normal subjects, an incidence of 66.7 per cent. The results obtained in five of these twelve patients indicate that the fall in arterial blood pressure was unaccompanied by any change in cardiac output or right ventricular pressure.

2. Eighteen of the twenty-three patients with cardiovascular disease showed a fall in arterial blood pressure, an incidence of 78.3 per cent. It was apparent, however, that in these cardiac patients the subsequent readjustments

in the circulation were dependent upon the physiologic status of the patient. In patients with normal cardiac output, no change in this determination was measurable. Patients with low cardiac outputs and elevated right ventricular systolic pressures responded with a shift toward more normal values.

3. It is suggested tentatively that the fall in arterial blood pressure following quinidine is due in large measure to peripheral vasodilatation. Some evidence for an effect on the myocardium is also presented.

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# II. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN LARGE ANTEROLATERAL INFARCTS

GORDON B. MYERS, M. D., HOWARD A. KLEIN, M. D., AND
TOMIHARU HIRATZKA, M.D.
DETROIT, MICH.

OBSTRUCTION to the flow of blood through the anterior descending coronary artery and its branches characteristically produces a large infarct of the apical one-third to two-thirds of the anterior wall of the left ventricle which almost invariably extends into the septum, usually into the apical one-third to one-half of the lateral wall, often into the apical one-third of the posterior aspect of the left ventricle, but seldom crosses over into the right ventricle.[1-3] In animals with infarcts of this type, produced by ligation of the anterior descending branch of the left coronary artery, Wilson and associates[4,5] accurately localized the position of the lesion through multiple epicardial leads. The findings in multiple precordial and unipolar limb leads have been described for large anterior infarcts in human subjects,[6-9] but have been carefully correlated with those at autopsy in only a few cases.[6,10,11]

A study, therefore, has been undertaken to determine the accuracy and limitations of multiple precordial and unipolar limb leads in the detection of extensions of large anterior infarcts into the lateral and posterior walls of the left ventricle, into the septum, and into the right ventricle, and their dependability for the estimation of the distribution of the infarct between the endocardial and epicardial surfaces of the underlying wall. The methods of electrocardiographic and pathologic study have been described.[12] In a series of 161 cases in which multiple precordial and limb leads were taken during life and in which myocardial infarction was accurately localized at autopsy, there were sixty-four patients with a large anterior infarct which extended into other portions of the left ventricle. The infarct continued into the apical one-third or more of the lateral wall in fifty-seven cases, extended into the septum in fifty-nine, crossed over into the anterior wall of the right ventricle in five cases, and extended through the septum or around the tip of the left ventricle to involve the apical one-third or more of the posterior wall in thirty-seven cases. The electrocardiographic findings have been analyzed in detail for each case and have been correlated with the area of involvement of the anterior, lateral, and posterior walls of the left ventricle, the septum, and the right ventricle, with the distribution of the lesion between endocardium and epicardium, and with a pathologic estimate of the age of the infarct.

From the Departments of Medicine and Pathology of Wayne University College of Medicine, and City of Detroit Receiving Hospital.
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To exemplify and summarize the correlation between the electrocardiographic findings and the various ramifications of the infarct at autopsy, the cases have been classified into three groups, which will be considered in separate reports. This manuscript comprises a detailed analysis of thirty cases, which collectively illustrate the various electrocardiographic patterns associated with infarction of the apical portion of the anterior and lateral walls of the left ventricle, and includes a summary, correlating the electrocardiographic and pathologic findings in all fifty-seven cases with a large anterior infarct extending into the apical one-third or more of the lateral wall. In the next communication, a similar analysis will be made of eighteen cases of coexistent anteroposterior infarction and a summary will be given of all thirty-seven cases in which the anterior infarct extended through the septum or around the tip of the left ventricle to the apical one-third or more of the posterior aspect. In the next report nineteen cases of infarction of the interventricular septum will be analyzed, and the findings in all cases in which a large anterior infarct extended into the septum or right ventricle will be summarized.

## CASE REPORTS

CASE 21.—A man, 69 years of age, was well until November, 1943, when he began to have paroxysmal nocturnal dyspnea. Congestive failure supervened, leading to hospital admission on Dec. 19, 1943. No clinical evidence of myocardial infarction was found during his hospital stay. In the spring of 1944 he began to have brief attacks of stabbing precordial pain. Following an exceptionally severe attack in August, 1944, decompensation recurred and led to hospitalization elsewhere. Late in October, another attack of prolonged stabbing precordial pain occurred, followed by cardiac failure and readmission on October 30. Orthopnea persisted in spite of therapy and bronchopneumonia developed, ending in death on the twelfth hospital day.

*Electrocardiographic Findings.*—Electrocardiograms obtained during his three admissions are reproduced in Fig. 1. The tracing of Dec. 23, 1943, was taken after the administration of a total of 1.5 Gm. digitalis during the three preceding days. The tall R wave and slightly delayed intrinsicoid deflection in Leads $V_4$ and $V_6$ were typical of left ventricular hypertrophy. The RS-T segment and T wave exhibited evidence of full digitalis effect. Maintenance doses of 0.1 Gm., daily, were continued for the rest of his life. The electrocardiogram of September 28 was taken about one month after the first attack of prolonged precordial pain. The last two tracings were obtained after the second attack. The pattern in Lead $V_2$ was practically constant throughout and was characterized by a small R, a deep S, an elevated RS-T junction, and upright T wave consistent with the changes produced by left ventricular hypertrophy in leads from the right side of the precordium. The replacement of the tall R originally present in Lead $V_4$ by a QS complex was diagnostic of infarction of the apical portion of the anteroseptal wall of the left ventricle, particularly in view of the persistence of the initial R in Lead $V_2$. Attention is directed to the presence of a distinct notch on both limbs of the QS complex of Lead $V_4$ on September 28, to the disappearance of the final notch in the tracing of October 31, and to the absence of both notches on November 6. The notches were probably due to activation of islands of responsive muscle in the infarcted anterior wall, and their disappearance after the second attack suggested reinfarction in the same area. A QS pattern of central zonal type was also present in Lead $V_3$ of the final tracing. Lead $V_6$ of the second and fourth tracings displayed a Q wave of 2.0 mm., which was 25 to 33 per cent of the amplitude of the succeeding R wave. This pattern, taken in conjunction with the fact that the R wave had undergone a 66 per cent reduction in voltage since December, 1943, was construed as evidence of extension of the infarct into the subendocardial portion of the lateral wall of the left ventricle. The changes in Leads $aV_L$ and I were roughly parallel to those in $V_6$. A more typical marginal pattern was recorded in Lead $V_5$, which exhibited

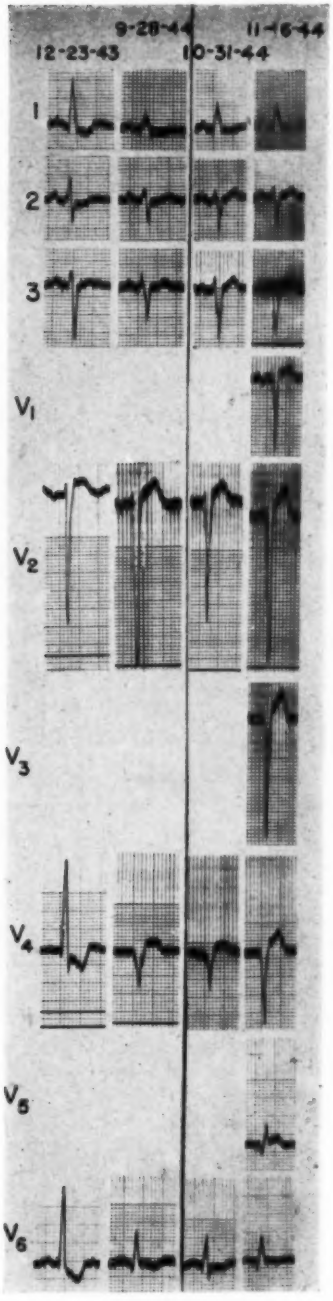


Fig. 1.—Serial electrocardiograms of Case 21 before and after development of anterolateral infarction.

a broad Q wave, 2.5 mm. in depth, followed by a slurred R, 5.0 mm. tall, an elevated RS-T junction, and monophasic, upright T wave, suggestive of the injury phase of reinfarction.

*Pathologic Findings.*—The heart weighed 720 grams and exhibited marked left ventricular hypertrophy and moderate secondary right ventricular hypertrophy. A large organized infarct of at least two months' duration was found in the anterolateral wall, as outlined in Fig. 2. Although the infarct extended through the entire wall, the subepicardial portion was somewhat patchy in the third and fourth segments. There was definite evidence of recent reinfarction of the lateral portion of the apex. The location and age of the infarct corresponded closely to that predicted from the serial electrocardiograms.

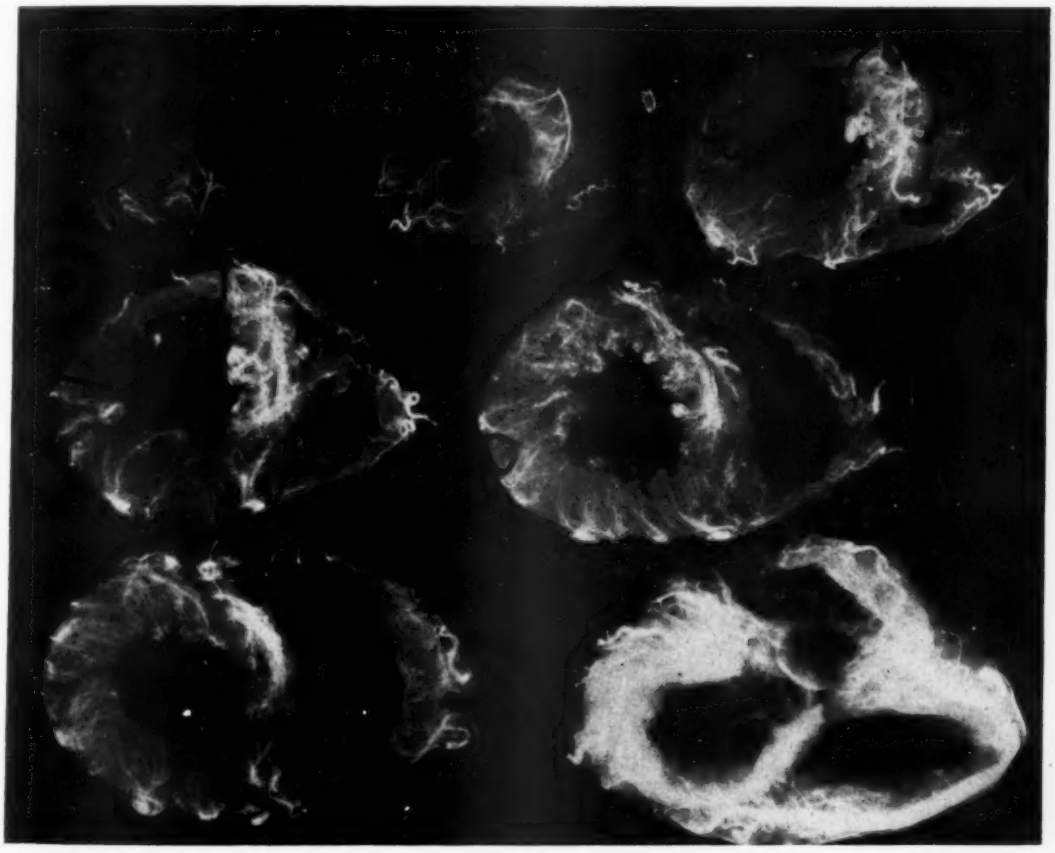

Fig. 2.—Roentgenogram of the injected heart of Case 21.

CASE 22.—A man, 49 years of age, had had cough, hemoptysis, dyspnea, and right-sided pleural pain for two weeks, but gave no definite history of myocardial infarction. Physical examination revealed bronchopneumonia, left ventricular hypertrophy, and a blood pressure of 220/110. Patient died suddenly on the tenth hospital day.

*Electrocardiographic Findings.*—An electrocardiogram obtained one hour after hospital admission and before the administration of digitalis is reproduced in Fig. 3,*A*. A definite R wave was present in Lead $V_1$, a minute R was barely detectable in $V_2$, and a QS complex was present in Leads $V_3$, $V_4$, and $V_5$. Lead $V_6$ displayed an initial Q, which was about 20 per cent of the suc-

ceeding R wave, whereas Lead $aV_L$ showed a Q of 3.0 mm. and an R of 26 millimeters. The QS complex in Leads $V_3$, $V_4$, and $V_5$ was indicative of a transmural infarct of the anteroseptal and anterolateral aspects of the apex, and the marked RS-T elevation in these leads pointed tc a very recent lesion. The standard leads showed evidence of left ventricular hypertrophy, but were not diagnostic of recent infarction. Two subsequent tracings, taken on the sixth and eighth hospital days, showed the usual evolution in T waves, but no significant change in QRS.

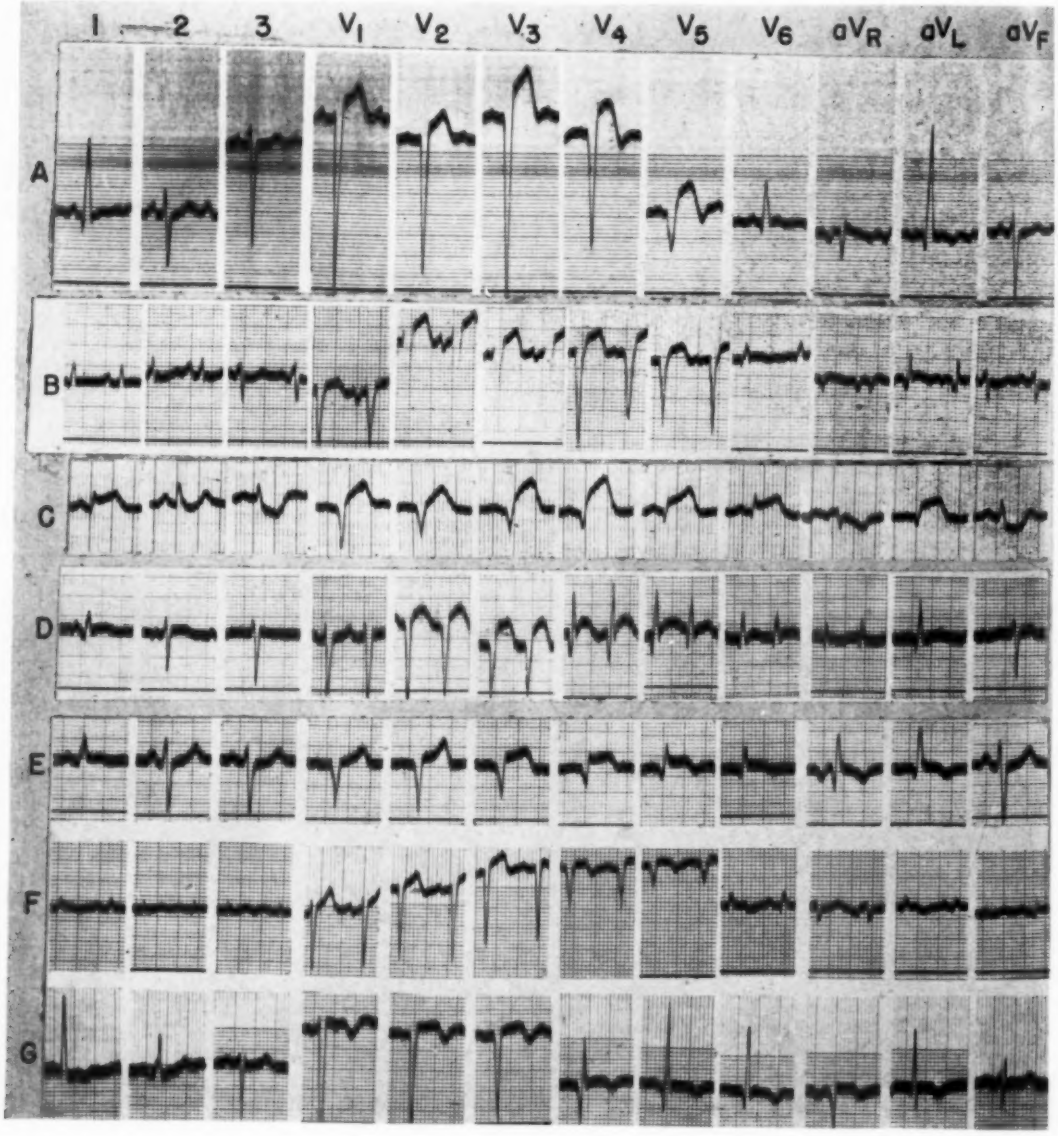


Fig. 3.—Recent anterolateral infarction. *A*, Case 22; *B*, Case 23; *C*, Case 24; *D*, Case 28; *E*, Case 29; *F*, Case 31; *G*, Case 33.

*Pathologic Findings.*—The heart weighed 721 grams and exhibited marked left ventricular hypertrophy. A recent infarct involved the entire apical one-third of the anterolateral wall of the left ventricle and septum and extended a little higher in the subendocardial one-half of the anterior wall, as outlined in Fig. 4. Death was due to rupture of the anterior wall just above the apex. Although a QS pattern would have been expected in association with the transmural infarction, the noteworthy feature of this case was the consistent finding of a QS in three precordial leads ($V_3$, $V_4$, and $V_5$), resulting from a relatively small area of transmural infarction confined to the apical one-third of the left ventricle. The lack of electrocardiographic signs of septal infarction may have been due to limitation of the lesion to the apical one-third. The failure of Lead $aV_F$ to show signs of infarction of the posteroapical portion of the left ventricle was attributable to horizontal position with subdiaphragmatic transmission of potential variations of the posterior inferior surface of the right rather than those of the left ventricle.

CASE 23.—A previously healthy man, 64 years of age, had had several transient attacks of retrosternal pain during the preceding fortnight, and on the night of admission to the hospital was awakened by a much more severe and prolonged attack. Hospital course was uneventful until the twelfth day, when he died during sleep.

*Electrocardiographic Findings.*—An electrocardiogram obtained twelve hours after the onset of the protracted retrosternal pain is reproduced in Fig. 3,*B*. The prominent intrinsicoid deflection and diphasic contour of the P waves in Leads $V_1$ and $V_2$ suggested that the electrode was in the vicinity of the right atrium and indicated that the ventricular complex in these leads reflected principally the potential variations of the right side of the septum and the right ventricle. Attention is directed to the presence of an initial R wave in Leads $V_1$ and $V_2$, to the decrease in its amplitude in $V_3$, to the QS complex of central zonal type in $V_4$ and $V_5$, and to the abnormal QR of marginal zonal type in Leads $V_6$ and $aV_L$. These findings were indicative of infarction of the anterior and lateral wall of the apical portion of the left ventricle. The elevation of the RS-T junction, straightening of the segment, and monophasic, upright T wave in all precordial leads and in Lead $aV_L$ pointed to a recent infarct in the stage of injury. It is noteworthy that a definitely abnormal Q wave was present in Lead $aV_L$, but was cancelled out in Lead I because of an equivalent initial negativity of the right arm.[13] The standard leads showed a slurred QRS of low voltage, but were not diagnostic of infarction.

*Pathologic Findings.*—The heart weighed 571 grams as a result of left ventricular hypertrophy. A very large, recent transmural infarct covering the entire anterior wall of the left ventricle, extending into the lateral portion of the apex, and involving the entire septum in the apical two segments and the anterior one-half in the remainder, was clearly outlined in the roentgenogram reproduced in Fig. 5. The involvement of the anteroseptal and anterolateral aspect of the apex was adequately represented by the QS in Leads $V_4$ and $V_5$ and the abnormal QR of Leads $V_6$ and $aV_L$. The infarction of the septum and adjacent anteroseptal wall was suggested by the RS-T displacement in Leads $V_1$, $V_2$, and $V_3$, but was so extensive that it should have given rise to bundle branch block, or at least to abnormal QS deflections in the first three precordial leads. Because of the short interval between the onset of the attack and the recording of the electrocardiogram, it is possible that degenerative changes had not progressed sufficiently in the septum and basal two-thirds of the anteroseptal wall to obliterate their response to the activating impulse. It is also possible that the original infarct was more like that in Case 22 (Fig. 4), and that extension into the base of the anterior wall and septum took place during the twelve-day interval before death. Since no subsequent tracings were obtained, the explanation for the discrepancy between electrocardiographic and pathologic findings is left unsettled. If, at the time of the electrocardiogram, the infarct had attained the size demonstrated at autopsy, the R waves in Leads $V_1$, $V_2$, and $V_3$ may have been contributed by activation of the outer wall of the right ventricle. A small, completely healed posterior infarct was also found at autopsy, as indicated by the broken lines in Fig. 5, but was not detected electrocardiographically, perhaps because the heart was in horizontal position.

Fig. 4.—Roentgenogram of the injected heart of Case 22.

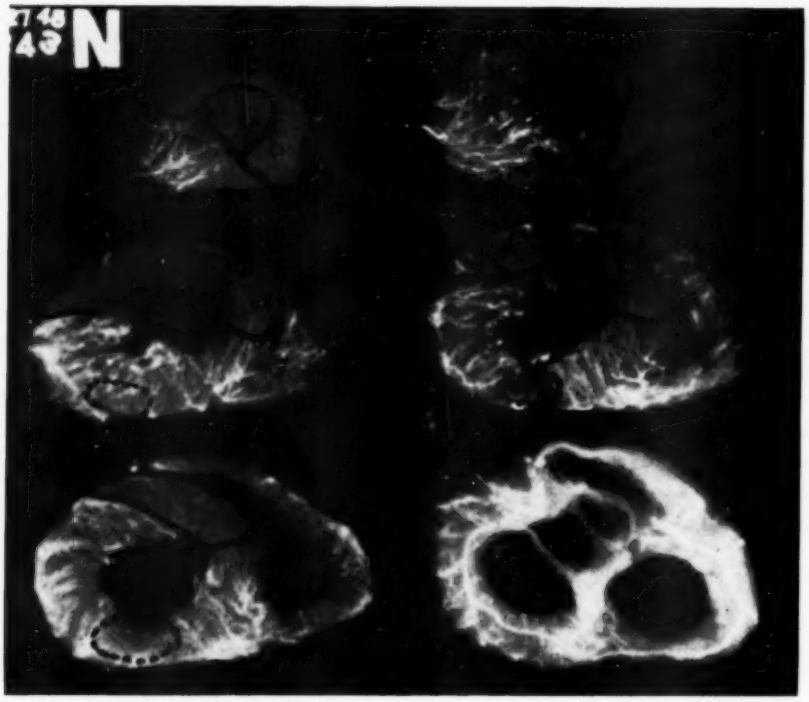


Fig. 5.—Roentgenogram of the injected heart of Case 23, showing a recent extensive anterolateral infarct and an old posterior infarct.

CASE 24.—A woman, 54 years of age, had had angina pectoris for five years and was admitted to the hospital because of a very severe attack of oppressive retrosternal pain of five and one-half hours' duration. The patient remained in circulatory collapse and expired fifty-four hours later. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained ten hours after the onset of the present illness is reproduced in Fig. 3,*C*. From the presence of a QS complex, markedly elevated RS-T junction, and monophasic, upright T wave in Leads $V_1$, $V_2$, $V_3$, $V_4$, $V_5$, and $aV_L$, and an abnormal QR complex and elevated RS-T junction in $V_6$, a diagnosis was made of a large, recent infarct, involving the anterior and lateral walls of the left ventricle and extending into the septum. The pattern in Lead $aV_L$ was carried over into Lead I, so that a diagnosis of anterolateral infarction could readily be made from the standard leads. There was marked reciprocal depression of the RS-T junction in Leads $aV_F$ and III.

*Pathologic Findings.*—The heart weighed 300 grams and displayed a rupture in the anterior wall with hemopericardium. A recent transmural infarct was found, involving almost the entire anterior wall and extending into the septum and lateral aspect of the apex, comparable to that in Case 23 (Fig. 5). There was good correlation between the electrocardiographic findings and the extensive infarct of the anterolateral wall of the left ventricle. The absence of the R wave in Leads $V_1$ and $V_2$ was probably a manifestation of the septal involvement.

CASE 25.—A woman, 51 years of age, with diabetes, began to have attacks of prolonged retrosternal oppressive pain four days before hospital admission. She was brought to the hospital in circulatory collapse and died the following day.

*Electrocardiographic Findings.*—Electrocardiograms were obtained on the first and second hospital days, but are not reproduced because of the striking similarity of the QRS-T pattern to that in Case 24 (Fig. 3,*C*). Auricular tachycardia with a rate of 165 per minute was found in both tracings; a 1 : 1 ventricular response was present in the first and complete auriculoventricular block in the second tracing. A diagnosis of a large, recent infarct of the anterolateral wall of the left ventricle was made. Extension into the septum was postulated to account for the QS pattern in leads over the right ventricle and for the terminal auriculoventricular block.

*Pathologic Findings.*—The heart weighed 495 grams and showed a recent transmural infarct similar in extent and distribution to that in Case 23 (Fig. 5). There was no evidence of atrial infarction. The terminal auriculoventricular block might have been related to the extensive septal infarction. The QRS-T pattern in the precordial and limb leads corresponded closely with the location of the infarct in the septum and anterior and lateral walls of the left ventricle.

CASE 26.—A man, 48 years of age, who had had no previous cardiovascular symptoms, was seized with a vise-like retrosternal pain and was hospitalized one and one-half hours later. The blood pressure was 220/150. Death occurred eight hours after the onset of the retrosternal pain.

*Electrocardiographic Findings.*—An electrocardiogram was obtained three hours after the onset of the pain, but is not reproduced because of its close resemblance to that in Case 24 (Fig. 3,*C*). A QS complex of the central zonal type, markedly elevated RS-T junction, and monophasic, upright T wave were present in all six precordial leads and in $aV_L$ and led to a diagnosis of very large, recent infarct of the anterior and lateral wall of the left ventricle extending into the septum.

*Pathologic Findings.*—The heart weighed 596 grams and showed a rupture of the anteroapical wall with hemopericardium. There was a very large, recent transmural infarct, which involved the anterior wall and septum, as in Case 23 (Fig. 5), but extended around the entire circumference of the left ventricle in the two apical segments. The findings in the six precordial leads and in $aV_L$ corresponded closely with the transmural infarction of the anterior and lateral walls of the left ventricle. Infarction of the septum was considered responsible for the QS complex and RS-T elevation in Leads $V_1$ and $V_2$, but did not cause prolongation of the QRS interval. The involvement of the posterior portion of the apex was not revealed by Lead $aV_F$ or by Leads II and III.

CASE 27.—A man, 59 years of age, gave a history of one attack of transient retrosternal oppression one month previously and a second, much more prolonged attack of more severe pain on the evening of hospital admission. Death occurred on the fourth hospital day.

*Electrocardiographic Findings.*—An electrocardiogram is not reproduced because of its resemblance to that in Case 23 (Fig. 3,*B*), except in Leads $V_2$ and $V_3$, where it exhibited a QS rather than an RS complex. The findings were typical of a large, recent infarct of the anterior and lateral walls of the left ventricle.

*Pathologic Findings.*—The heart weighed 465 grams and exhibited a very large recent infarct, almost identical in location with that in Case 26. Although transmural infarction of the lateral wall was found in the apical two segments in both cases, a QS pattern was recorded in Leads $V_5$, $V_6$, and $aV_L$ in Case 26 and only in Lead $V_5$ in this case. The difference may have been due to differences in cardiac position. The heart in Case 26 was moderately rotated in a clockwise direction, which would favor transmission of the potential variations of the large anterior portion of the infarct toward the axilla, whereas the heart in the present case was rotated counterclockwise, which would facilitate transmission of the potential variations of the uninfarcted portion of the lateral wall into the axilla, thus accounting for the upright portion of the abnormal QR complex in Leads $V_6$ and $aV_L$. The horizontal position of the heart in this case probably accounted for the absence of signs of the posteroapical infarct in Lead $aV_F$.

CASE 28.—A man, 63 years of age, was admitted with a history of a productive cough of four months' duration and a 50-pound weight loss referable to bronchiogenic carcinoma. During the second hospital week, auricular fibrillation developed and dyspnea increased, but no definite history of constrictive pain could be elicited. Death occurred on the twenty-fourth hospital day.

*Electrocardiographic Findings.*—An electrocardiogram taken on the sixteenth day, after the administration of 2.8 Gm. digitalis during the preceding week, is reproduced in Fig. 3,*D*. A previous tracing taken three days earlier had shown auricular fibrillation and a similar QRS-T pattern. Sinus rhythm with abnormal diphasic P waves was present on the sixteenth day, when the standard leads were recorded, and auricular fibrillation recurred just before the precordial leads were taken. A 3.0 mm. R wave, an isoelectric RS-T junction, and normal, upright T wave were recorded in Lead $V_1$ and contrasted sharply with the abnormalities in the remaining leads. A QS deflection was found in Leads $V_2$ and $V_3$ and a QR complex with an abnormally deep Q was evident in Leads $V_4$, $V_5$, and $V_6$. The QRS changes were indicative of a large, transmural anterior infarct, which extended subendocardially into the lateral wall. On the basis of the displacement and typical domelike contour of the RS-T segment and monophasic, upright T wave, it was thought that the infarct was of recent origin, but too little attention was given to the absence of serial changes in three tracings taken over a period of ten days. Signs suggestive of a recent, anterolateral infarct were present in the standard leads.

*Pathologic Findings.*—Death was due to bronchiogenic carcinoma, which had metastasized to the right atrium and pericardial sac and had led to a generalized fibrinous pericarditis. The heart weighed 459 grams and exhibited an old, completely healed infarct of anterior and anterolateral walls of the left ventricle, occupying a position almost identical to that in Case 21 (Fig. 2). The dense part of the infarct was confined to the subendocardial one-half of the wall, but fingerlike extensions reached the epicardium. Multiple microscopic sections revealed no evidence of recent infarction. The QRS pattern in the precordial leads corresponded rather closely to the location of the infarct at autopsy, but the RS-T and T-wave abnormalities, which had led to a mistaken diagnosis of a recent infarct, were probably due to the pericarditis. Fixed RS-T abnormalities associated with an old infarct and independent of the pericarditis constituted a possible alternative.

CASE 29.—A previously healthy man, 66 years of age, was suddenly stricken with severe, oppressive retrosternal pain which radiated to both arms and led to hospitalization six and one-half hours later. No cardiac glycosides were given. Death occurred from bronchopneumonia on the twenty-eighth day.

*Electrocardiographic Findings.*—An electrocardiogram obtained nineteen hours after the onset of the present illness is reproduced in Fig. 3,*E*. A QS complex was present in Leads $V_1$, $V_2$, and $V_3$ and a broad Q, abnormally large in relation to the subsequent R, was found in $V_4$, $V_5$, and $V_6$. The abnormalities in the initial phase of the QRS were indicative of a large anterior infarct, extending into the septum and into the lateral wall of the left ventricle. The RS-T junction was moderately elevated in Lead $V_2$, but the segment displayed the normal upward concavity. However, in Leads $V_3$, $V_4$, $V_5$, and $V_6$ there was not only an abnormal RS-T elevation, but also an RS-T and T-wave contour typical of recent infarction. The inverted P and QR complex of Lead $aV_L$ and the exceptionally tall late R wave in $aV_R$ suggested that the potential variations of the posterobasal aspect of the left ventricle were transmitted to both upper extremities. Because of the simultaneous reference of positive potentials to both upper extremities, the late R of Lead I was relatively small in amplitude and the findings in this lead were consequently suggestive of infarction.

*Pathologic Findings.*—The heart weighed 380 grams and exhibited a recent organizing infarct, involving the entire apical two-thirds of the anterior wall, extending into the lateral aspect of the apex and also through the septum to the posterior part of the apex, as outlined in Fig. 6.

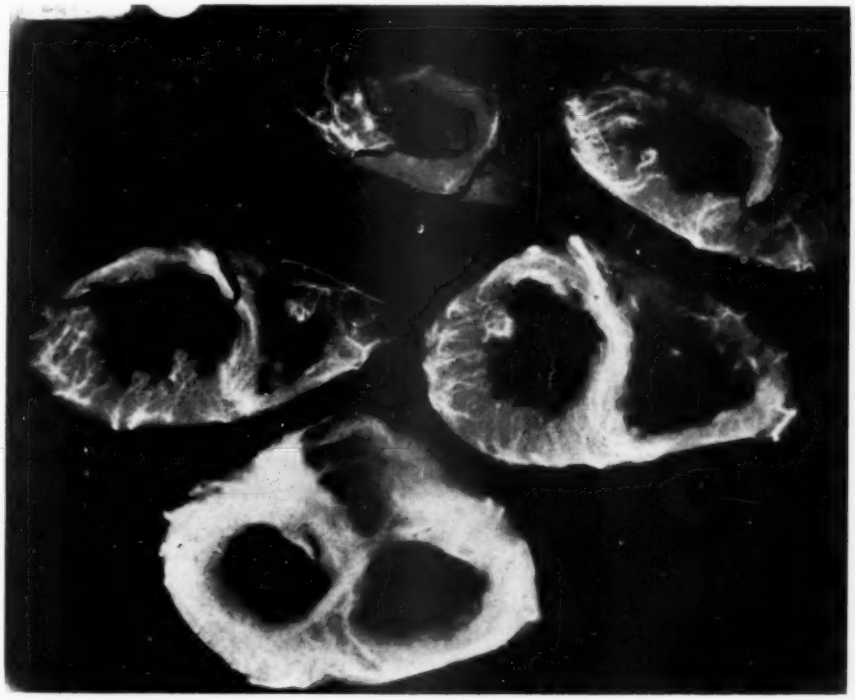

Fig. 6.—Roentgenogram of the injected heart of Case 29.

The infarct was transmural in its anterior portion and involved the subendocardial one-half in its lateral portion. The electrocardiographic findings in the first four precordial leads corresponded closely with the anterior and septal portions of the infarct, but those in $V_5$ and $V_6$ were more marked than would have been expected from the limitation of the lateral portion of the infarct to the apical segment. The absence of signs of the posteroapical infarction from Lead $aV_F$ was probably due to horizontal position of the heart.

CASE 30.—A woman, 64 years of age, who had had hypertension for years, gave a typical history of myocardial infarction nine hours before hospitalization. Death occurred fifteen and one-half hours after admission.

*Electrocardiographic Findings.*—An electrocardiogram was obtained fourteen hours after the onset of the pain, but is not reproduced because of its similarity to that in Case 29 (Fig. 3,*E*). This electrocardiogram was diagnostic of a large, recent anterior infarct, extending into septum and lateral wall.

*Pathologic Findings.*—The heart weighed 437 grams and exhibited a recent transmural infarct, similar in position to that in Case 29 (Fig. 6), except that it extended into the apical one-half of the lateral wall. The electrocardiogram conformed closely with the lesion of the anterior, septal, and lateral walls, but failed to reveal the infarction of the posterior aspect of the apex because of the horizontal position of the heart.

CASE 31.—A man, 62 years of age, had been in good health until the day before hospital admission, when he had an attack of retrosternal pain, lasting ten minutes. The pain recurred on the afternoon of admission and lasted two hours. After a brief hiatus, it returned in the evening and necessitated hospitalization. Blood pressure was at shock levels during the eleven-day period in the hospital.

*Electrocardiographic Findings.*—An electrocardiogram obtained twenty-one hours after the second attack of pain and before the administration of cardiac glycosides is reproduced in Fig. 3,*F*. Lead $V_1$ showed an initial R of 2.0 mm. and Lead $V_2$, an initial R of 0.5 millimeter. A QS complex present in Leads $V_3$, $V_4$, and $V_5$ was indicative of the central zone, whereas a QR complex of low voltage in Leads $V_6$, $aV_L$, and $aV_F$ was probably representative of a marginal zone of subendocardial infarction. Thus, the electrocardiogram gave evidence of a large anterior infarct, which extended into the lateral and posterior aspects of the apex, and the T-wave pattern indicated that it was of recent origin. The standard leads were of exceptionally low voltage and were strongly suggestive of infarction.

*Pathologic Findings.*—The heart weighed 480 grams and showed a large infarct, involving the apical two-thirds of the anterior aspect of the left ventricle and the apical one-third of the lateral and posterior aspects and the apical one-half of the interventricular septum. The infarct was transmural on the anterior surface and involved the subendocardial one-half in the lateral and posterior aspects. The location of the infarct was thus comparable to that in Case 29 (Fig. 6). In addition, there was an old, completely healed subendocardial infarct in the anteroseptal area at the base of the ventricle just proximal to the recent infarct. There was good correlation between the position of the recent infarct, as determined from the electrocardiogram and as demonstrated at autopsy, except for the fact that the electrocardiogram showed no definite signs of septal involvement.

CASE 32.—A man, 57 years of age, who had had hypertension for sixteen years, gave a history of an acute onset of painless dyspnea three weeks before admission to the hospital. Despite digitalization by his family physican, progressive failure developed. The patient was moribund on admission and died twenty-two hours later.

*Electrocardiographic Findings.*—An electrocardiogram resembled the last tracing in Case 21 (Fig. 1), and, consequently, is not reproduced. A diagnosis was made of a large, recent anterior infarction, extending into the lateral wall of the apex. The standard leads showed evidence of left ventricular hypertrophy, but were not diagnostic of infarction.

*Pathologic Findings.*—The heart weighed 704 grams and showed a recent infarct of the anterolateral wall of the left ventricle, resembling that in Case 21 (Fig. 2). This was partially superimposed upon an older anterior infarct, which extended into the septum in the four apical segments. The electrocardiogram revealed the anterolateral infarct, but failed to show definite evidence of the septal lesion.

CASE 33.—A man, 50 years of age, was admitted to the hospital in advanced congestive heart failure with a history of dyspnea and intermittent, stabbing retrosternal pain during the antecedent six months. There were physical signs of syphilitic aortic insufficiency. Death occurred forty-six hours after admission.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the first hospital day, after 0.6 mg. of digitoxin, is reproduced in Fig. 3,*G*. Attention is directed to the 2.0 mm. initial R wave in Lead $V_1$, the QS deflection in $V_2$ and $V_3$, and the QR complex with abnormal Q in $V_4$, $V_5$, and $V_6$. From the findings in Leads $V_4$, $V_5$, and $V_6$, the presence of an organizing subendocardial infarct in the anterolateral wall of the apex was postulated, and from the findings in $V_2$ and $V_3$, the presence of an organizing transmural infarct higher in the anteroseptal wall was predicted. The limb leads showed signs compatible with an ischemic zone or with left ventricular hypertrophy, but not diagnostic of infarction.

*Pathologic Findings.*—The heart weighed 518 grams as the result of left ventricular hypertrophy secondary to syphilitic aortic insufficiency. There was an organizing infarct of the anterolateral wall of the three apical segments, closely comparable in size and position with that in Case 22 (Fig. 4). This infarct involved the subendocardial half of the lateral wall in the apical two segments, thus conforming with the electrocardiographic findings. However, the distribution in the anterior wall was the reverse of that predicted from the electrocardiogram in that the infarct was transmural in the apical two segments and subendocardial in the third segment. The QS complex in Leads $V_2$ and $V_3$ could not have been derived from the intact basal one-half of the anterior wall. The counterclockwise rotation revealed in the unipolar extremity leads may have displaced the transitional zone sufficiently to the right so that Leads $V_2$ and $V_3$ reflected the potential variations of the anteroseptal portion of the apex, which was the site of the transmural infarct, whereas Leads $V_4$, $V_5$, and $V_6$ reflected the potential variations of the anterolateral aspect of the apex, which was the site of a subendocardial infarct. It is also possible that the QS complex in $V_2$ and $V_3$ was a manifestation of the septal infarction. The normal initial R in $V_1$ is against this hypothesis, but might have been derived from activation of the free wall of the right ventricle.

CASE 34.—A previously healthy man, 47 years of age, was suddenly seized with constrictive retrosternal pain, radiating down both arms, followed by syncope and circulatory collapse. He died on the eleventh hospital day. No cardiac glycosides were given.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the first hospital day, approximately twenty-four hours after the onset of the pain, is reproduced in Fig. 7,*A*. The initial phase of the QRS was upright in all precordial leads. This R wave was 3.0 mm. in amplitude in Lead $V_1$ and 1.0 mm. in $V_2$, and then fell off to 0.5 mm. in $V_3$, $V_4$, and $V_5$, and then increased to 1.0 mm. in Lead $V_6$. The decrease in the amplitude of the R wave, as the electrode was moved from positions over the right ventricle to positions over the left ventricle, was abnormal and, coupled with the marked RS-T elevation and monophasic, upright T wave, led to the diagnosis of a recent, large anterolateral infarct. To explain the unusual finding of an initial upright rather than a downward deflection in leads over the infarct, it was postulated that the infarct either was patchy in distribution through the wall or failed to involve a thin subendocardial layer of muscle. Left bundle branch block was excluded by the absence of prolongation of the QRS interval. Two further electrocardiograms on the third and ninth hospital days showed essentially the same QRS pattern as in the original tracing, including an abnormally small but distinct initial R in the last five precordial leads. Lead $aV_L$ displayed a QR complex with borderline Q of .02 second duration and 25 per cent of the succeeding R, followed by an elevated RS-T junction and inverted T wave. The QRS-T pattern in Lead $aV_L$ was compatible with the findings obtained over a marginal zone of subendocardial infarction. However, if the QRS-T pattern in $aV_L$ had been transmitted from the apical portion of the lateral wall to the left arm, the cardiac position should have led to the recording of an upright rather than an inverted P wave in Lead

$aV_L$.[13] The inverted P wave, prominent Q, tall late R, and sharply inverted T wave of Lead $aV_L$ simulated the pattern which may be obtained in normal subjects through esophageal leads at or slightly above the level of the atrioventricular groove. The potential variations of this region may be transmitted both to the left and the right arms when the heart is rotated about a transverse axis in such a way as to carry the apex backward and tilt the base upward. Backward rotation on a transverse axis was borne out in this case by the tall, late R wave in Lead $aV_R$, which was derived from activation of the posterobasal wall of the left ventricle. Because of the position of the heart in this case, the findings in $aV_L$ might have represented a normal variant and could not be regarded as diagnostic of infarction. The pattern most strongly suggestive of infarction was found in standard Lead I. The Q wave in Lead I was similar to that in $aV_L$, but the R wave in Lead I was greatly reduced over that in $aV_L$ because positive potentials were being referred to both upper extremities during the latter part of cardiac activation and thus $R_1$ constituted the difference between the late R waves of Leads $aV_L$ and $aV_R$. The elevated $RS\text{-}T_1$ represented the reciprocal of the RS-T depression in $aV_R$. Since the Q wave registered through the left arm component of Lead I may have been a normal variant, the findings in the standard leads could not be regarded as pathognomonic of infarction.

*Pathologic Findings.*—The heart weighed 617 grams and showed a large, recent infarct, which involved the entire anterolateral wall, the left half of the septum and the subendocardial half of the posterior wall in the apical two segments, the free portion of the anteroseptal wall and adjoining anterior half of the left side of the septum in the third, fourth, and fifth segments, and the anterior half of the left side of the septum in the sixth segment, as indicated by the areas of avascularity in the roentgenogram (Fig. 8). Microscopic sections showed that the infarct extended through the entire thickness of the anterior wall, including the papillary muscles and subendocardial layer, and failed to substantiate the ante-mortem explanation for the initial R waves in the precordial leads. In view of the electrical position of the heart, the possibility was considered that the apex had been carried far enough backward to impair transmission of its potential variations to precordial Positions 3, 4, and 5, and thus indirectly favor transmission of the potential variations of more basal portions of the anterolateral wall to these regions. However, the fact that the anterior portion of the infarct involved almost the entire wall left little muscle at the base to serve as a source for the R wave and necessitated search for another explanation. Consideration was given to the possibility that the Purkinje network in the anterior half of the left side of the septum was destroyed by the infarct in this area. Under these circumstances, any residual intact muscle in the anterior half of the septum must have been activated by way of the Purkinje plexus of the right ventricle. Positive potentials resulting therefrom would have been transmitted toward the left side of the precordium and might have accounted for the initial R in Leads $V_3$, $V_4$, and $V_5$. Since the negative potentials would have been directed toward the right ventricular cavity, a small Q would have been expected preceding the RS complex of $V_1$. However, this Q might be eliminated if the impulse reached and started to activate the free wall of the right ventricle simultaneously with its penetration of the septum. Another feature which had to be rationalized with the foregoing hypothesis was the initial Q in left ventricular lead $aV_L$. Since the posterior half of the basilar two-thirds of the septum was intact at autopsy, the vector associated with its activation may have taken the usual direction, and, consequently, negative potentials may have been transmitted backward to the posterobasal wall of the left ventricle. Since the electrical position of the heart favored reference of the potential variations of the posterobasal aspect of the left ventricle to the left arm, the Q in $aV_L$ may have originated in this manner and may have represented a normal variant, unrelated to the infarct of the lateral aspect of the apex found at autopsy. If so, the QR complex of Lead I was also independent of the infarction. Although a dogmatic assertion as to the source of the Q waves in Leads $aV_L$ and I was impossible in this case, our contention that they might have represented a normal variant is supported by the findings in another patient, to be reported in detail later. Tracings in the recumbent position revealed abnormal QR complexes in Leads $aV_L$ and I, resembling those in the present case, whereas tracings in the erect position showed a notch at the base of the upstroke of the R in place of the Q wave. This patient subsequently came to autopsy and no evidence of myocardial infarction was found.

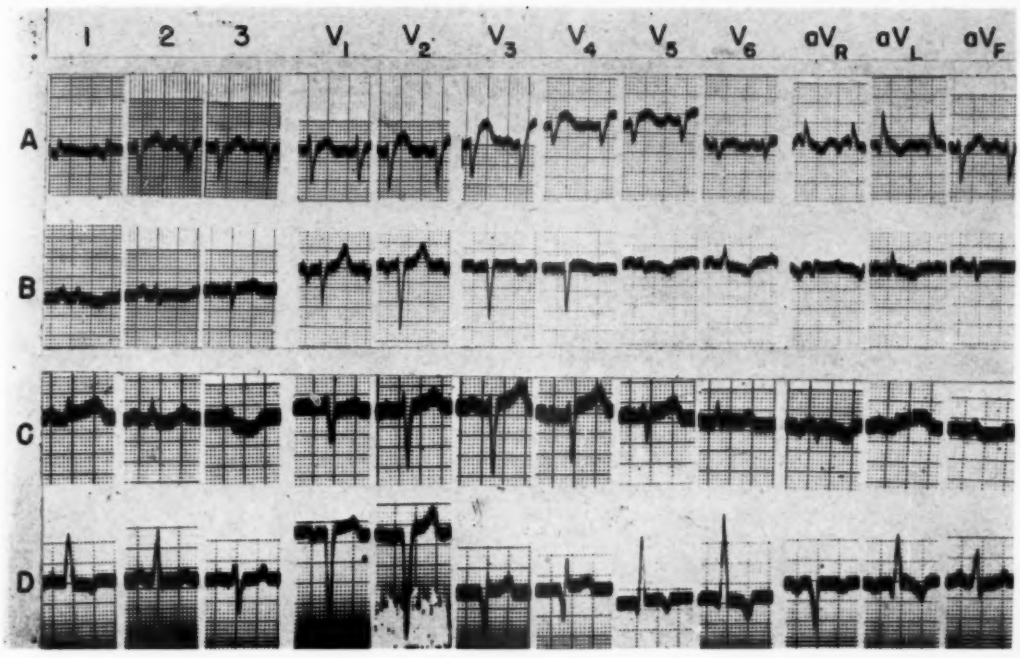


Fig. 7.—Recent anterolateral infarction with atypical QRS-T pattern. *A*, Case 34; *B*, Case 35; *C*, Case 36; *D*, Case 37.

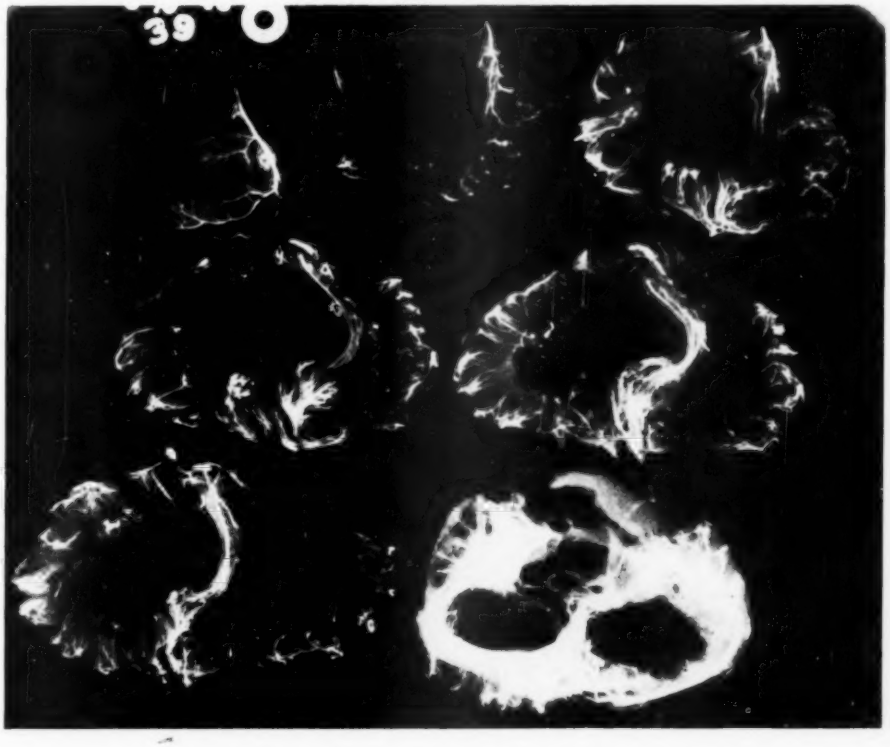


Fig. 8.—Roentgenogram of the injected heart of Case 34, showing recent anterolateral infarct demarcated by its avascularity.

CASE 35.—A man, 58 years of age, was suddenly stricken with prolonged retrosternal pain one month previously and had recurrent attacks of transient constriction during the interim, despite strict confinement to bed in his home. Following a second prolonged attack, he was admitted in shock and remained in circulatory collapse until death on the eighth hospital day. No cardiac glycosides were given.

*Electrocardiographic Findings.*—Electrocardiograms were obtained on the third and seventh hospital days, and the latter is reproduced in Fig. 7,*B*. The contour of the P waves in Leads $V_1$ and $V_2$ suggested that the electrode was in the vicinity of the right atrium. The QRS complexes were comparable to those in Case 34 in that the initial phase was upright in all precordial leads, but decreased from an amplitude of 1.0 to 2.0 mm. in Leads $V_1$ and $V_2$, to 0.5 mm. in $V_3$, $V_4$, and $V_5$, and then increased in $V_6$. The initial deflection was downward in Lead $aV_L$, but the QR complex in this lead was classed as borderline, since the Q was only 0.02 second in duration, 1.0 mm. in depth, and 25 per cent of the succeeding R. The dome-shaped RS-T segment and inverted T wave in Lead $V_4$ were strongly suggestive of the pattern associated with organizing infarct. The T wave was inverted in Leads $V_5$, $V_6$, and $aV_L$, but the slight depression of the RS-T junction in these leads was atypical. The standard leads were abnormal, but were not diagnostic of infarction. A diagnosis of a large anterolateral infarct was made and because of the preservation of the R wave, it was postulated that the infarct either was patchy in distribution or had spared a thin layer of subendocardial muscle.

*Pathologic Findings.*—The heart weighed 494 grams and exhibited evidence of an organizing infarct of approximately one month's duration, involving the anterior, lateral, and septal walls of the apical half of the left ventricle in a fashion similar to that in Case 34 (Fig. 8). This lesion extended subendocardially into the apical one-third of the posterior wall. In addition there was an infarct of approximately one week's duration, involving the posterobasal half of the left and right ventricles and the adjacent interventricular septum. Although the anterolateral infarct appeared to be transmural on gross examination, multiple microscopic sections in this case showed a few islands of intact muscle. These patches may have accounted for the minute initial R in the precordial leads over the left ventricle, particularly in view of the fact that the opposing negative potentials ordinarily derived from the posterior wall were reduced in this case by the extensive posterobasal infarction. The latter had been missed in the electrocardiographic interpretation, since Lead $aV_F$ of both electrocardiograms displayed an RS complex and low, upright T wave. The findings in $aV_F$ had been attributed to transmission of the potential variations of the right ventricle to the left leg, as the result of horizontal position. Since the basal portion of the right ventricle was infarcted, it is possible that the RS complex was derived from the intact apical portion of the right ventricle.

CASE 36.—A man, 65 years of age, gave a history of dyspnea and occasional brief attacks of retrosternal oppression on exertion during the antecedent two years, but had had no protracted retrosternal pain until the day of admission. He was brought to the hospital in shock seven hours after the onset of an exceptionally severe attack of retrosternal oppression. Blood pressure was unobtainable and profound circulatory collapse persisted, ending in death fifty-nine hours later.

*Electrocardiographic Findings.*—An electrocardiogram obtained eight hours after the onset of the pain is reproduced in Fig. 7,*C*. The initial phase of the QRS was upright in all precordial leads and measured 2.0 mm. in Lead $V_1$, 3.0 mm. in $V_2$, and dropped to 2.0 mm. in Leads $V_3$, $V_4$, and $V_5$, and increased to 5.0 mm. in $V_6$. The T wave was upright in all precordial leads and the RS-T segment displayed the normal upward concavity. The RS-T take-off was above the isoelectric line in all precordial leads, but was considered definitely abnormal only in $V_4$, where it was elevated 3.5 millimeters. The reduction in the amplitude of the R wave in Leads $V_3$, $V_4$, and $V_5$ and the abnormally elevated RS-T junction in $V_4$ were suggestive of a recent subepicardial or patchy transmural infarct, involving the anterior and anterolateral aspects of the left apex. The findings in Leads $aV_L$, $aV_F$, and I, II, and III were much more striking than those in the precordial leads. Lead $aV_L$ displayed an upright P wave, a QR complex of very low voltage, a high RS-T take-off, a straightened RS-T segment, and a monophasic, upright T wave typical of the stage of injury of recent lateral infarction. Lead I showed similar changes in the RS-T segment

and T wave, but was less typical of infarction than $aV_L$ because it lacked a Q wave. Lead $aV_F$ displayed reciprocal RS-T depression, which was carried over into Lead III. Because of the findings in Leads $aV_L$ and I, a diagnosis was made of recent infarction of the lateral wall of the left ventricle. Unfortunately, a second electrocardiogram was not obtained.

*Pathologic Findings.*—The heart weighed 534 grams and showed evidence of a recent, large infarct of the anterior wall of the left ventricle, the lateral aspect of the apex, and the interventricular septum, comparable in size and position to that in Case 34 (Fig. 8). Microscopic sections through the septum, anterior wall, and lateral aspect of the apex showed that the infarct was transmural. Thus, there was a considerable discrepancy between the surface area and thickness of the infarct, as predicted from the precordial electrocardiogram and the actual findings at autopsy. Two explanations for this discrepancy were given serious consideration. It is possible that the infarct was originally confined to the anterolateral aspect of the apex and extended during the fifty-eight hour period after the electrocardiogram was made. However, the profound degree of shock on admission suggested the presence of a large infarct, comparable in size to that found at autopsy. Since the electrocardiogram was obtained only eight hours after the onset of the pain, it seemed more likely that the myocardial degeneration had not progressed to the point of complete obliteration of the response to the activating impulse.

CASE 37.—A man, 47 years of age, had had chills and fever for two months and repeated attacks of retrosternal oppression for one week prior to hospital admission. Physical examination revealed evidence of mitral and aortic stenosis and insufficiency. Numerous petechiae and a positive blood culture for *Streptococcus viridans* established the diagnosis of subacute bacterial endocarditis. In spite of penicillin therapy, the patient expired on the seventh hospital day.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the first hospital day, before the administration of cardiac glycosides, is reproduced in Fig. 7,*D*. Attention is directed to the QS complex in Leads $V_1$ and $V_2$ and the QR deflection with abnormally large Q in $V_3$ and $V_4$ and with small but slurred and prolonged Q in $V_5$ and $aV_L$. On the basis of these findings, a diagnosis was made of a relatively large infarct of the septum and anterior wall, extending subendocardially into the lateral wall of the apex. The RS-T segments and T waves were atypical, but compatible with a recent infarct. The pattern in Lead $V_6$ and that in the standard leads was in keeping with left ventricular hypertrophy, but was not diagnostic of infarction.

*Pathologic Findings.*—The heart weighed 743 grams and showed evidence of chronic rheumatic mitral and aortic valvulitis complicated by subacute bacterial endocarditis. An organizing subendocardial infarct was found in the apical five-sixths of the anterior wall, the apical one-half of the lateral wall, the apical one-third of the posteroseptal wall of the left ventricle, and the apical two-thirds of the left side of the septum. The position of the infarct was similar to that in Case 23 (Fig. 5), except for limitation to the subendocardial half of the outer wall of the left ventricle and left half of the septum. No point was found where the infarct extended completely through the wall. The QS deflections in Leads $V_1$ and $V_2$ were apparently due to the septal lesion, and the QR complexes in $V_3$ and $V_4$ corresponded closely with the subendocardial infarct of the anteroseptal wall, whereas those in Leads $V_5$, $V_6$, and $aV_L$ could be correlated with the less extensive involvement of the lateral wall. The extension into the subendocardial one-third of the posteroseptal wall was not evident in $aV_F$, despite the fact that this lead reflected the potential variations of the left ventricle.

CASE 38.—A man, 57 years of age, was admitted to the hospital on March 12, 1947, for treatment of diabetes mellitus complicated by the Kimmelstiel-Wilson syndrome. He had had typical intermittent claudication, but denied other cardiovascular symptoms. On April 4 diarrhea developed and approximately ten stools daily were passed during the next five days. On April 8 he was suddenly seized with severe dyspnea unaccompanied by chest pain. Examination revealed a regular cardiac rate of 240, which was abruptly halved by carotid sinus pressure. Sinus rhythm soon returned spontaneously, but marked pulmonary edema persisted, leading to digitalization on April 10. Partial alleviation was obtained until 1:00 A. M. on April 15, when extreme orthopnea recurred and persisted until death fifteen hours later.

*Electrocardiographic Findings.*—Electrocardiograms are reproduced in Fig. 9. A routine tracing taken on March 31 showed a 2.0 mm. Q wave in Lead $aV_F$, which was approximately 15 per cent of the R wave in the same lead. Although this Q wave, when considered as an isolated finding, was not abnormal, the fact that it was followed by a slurred upstroke of 0.04 second duration suggested that the QR complex was abnormal. The pattern in Leads $aV_F$, II, and III

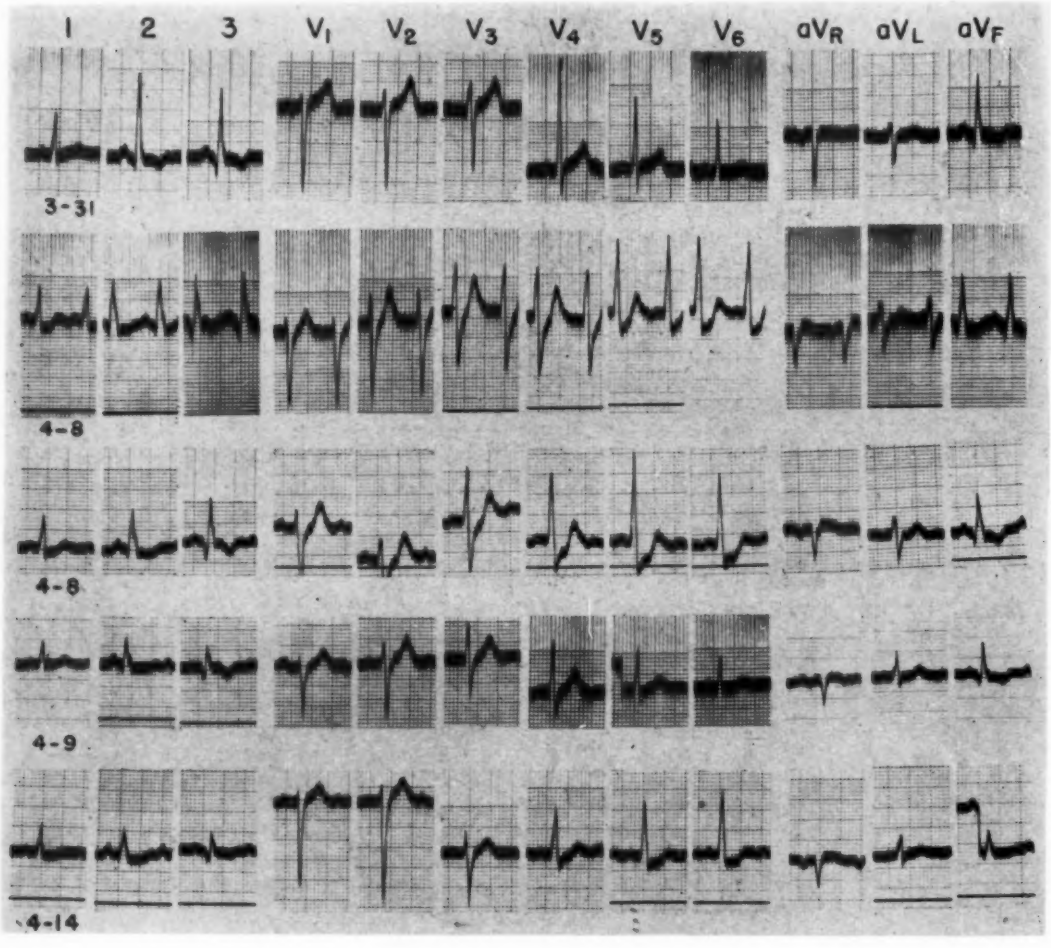


Fig. 9.—Serial electrocardiograms of Case 38, showing old posterior infarction in tracing made March 31, and subsequent ischemia of the subendocardial portion of the anterolateral wall.

of March 31 was compatible with, but not pathognomonic of a patchy subendocardial infarct of the posterior wall of the left ventricle. The QRS of the precordial leads of March 31 was entirely normal and the slight elevation of the RS-T junction in Leads $V_1$ through $V_5$ was considered normal in view of the relatively high voltage of the upright T wave in these leads and the upward concavity of the RS-T segment. In the first tracing, April 8, which was obtained two and one-half hours after the onset of the dyspnea, there was a regular ventricular rate of 120 per minute. The P waves appeared to correspond with those of the previous tracing, but close inspection of Leads $aV_F$, II, and III revealed an additional P wave in each cycle, coming immediately after the R and giving an auricular rate of 240. Therefore, a diagnosis of auricular tachycardia with 2:1

block was made. The most striking electrocardiographic change consisted in a marked depression of the RS-T junction, which amounted to 5.0 mm. in Lead $V_6$, 3.0 mm. in $V_5$ and $V_4$, and 2.0 mm. in Leads $V_3$ and $aV_F$. On the other hand, there was no significant change in the QRS complex or T wave, apart from a displacement of the transitional zone to the left. Another tracing taken three hours later on April 8 showed return of sinus rhythm, but persistence of the marked RS-T depression. The suddenly developing RS-T depression was attributed to acute ischemia of the subendocardial layer of muscle, most marked in the anterolateral aspect, but extending into the anteroseptal and posterior walls of the left ventricle. From the absence of significant QRS change, it was inferred that either the ischemia was patchy in distribution or it had not progressed to the point of interfering with the myocardial response to the activating impulse. The diagnosis of transient subendocardial ischemia was confirmed by the disappearance of the RS-T depression on April 9 and the return to a pattern closely resembling that of the control tracing of March 31. In the meantime the heart had shifted from a vertical to an intermediate position with concomitant reduction in the amplitude of the R wave in Lead $aV_F$ and consequent increase in the QR ratio to 33 per cent. The appearance of a disproportionately large Q wave in Lead $aV_F$ in conjunction with a slurred, abnormally prolonged ascending limb of the R wave led to a definite diagnosis of posterior infarction. RS-T depression reappeared in Leads $V_4$, $V_5$, and $V_6$ of the tracing of April 14, but its significance was debatable because of the administration of digitalis.

*Pathologic Findings.*—The heart weighed 450 grams and showed very marked coronary sclerosis. There was an old, completely healed infarct, extending in patchy fashion through the subendocardial two-thirds to three-fourths of the posterior wall, as represented by the broken line in Fig. 10. This infarct was apparently responsible for the pattern in Lead $aV_F$ of the control tracing of March 31. There was a very recent, ringlike infarct, involving the subendocardial one-half of the entire circumference of the left ventricle. By microscopic examination, this infarct was judged to be less than twenty-four hours in duration. If the age of the infarct was correctly interpreted, the transient RS-T depression on April 8 was attributable to acute ischemia of the subendocardial muscle, which later became infarcted. The last tracing on April 14 was obtained thirty hours before death, and it is problematic as to whether the acute subendocardial infarct demonstrated at autopsy was present at that time. However, both the history and microscopic findings suggested that the terminal subendocardial infarction occurred after the last electrocardiogram.

CASE 39.—A man, 80 years of age, gave a history of dyspnea and transient retrosternal distress on exertion for the preceding six months and was admitted to the hospital in shock, complicating a prolonged bout of severe retrosternal pain. He remained in circulatory collapse and died on the seventh hospital day.

*Electrocardiographic Findings.*—An electrocardiogram obtained about six hours after the onset of the second attack of prolonged retrosternal pain is reproduced in Fig. 11,*A*. A QS complex was found in Leads $V_1$ through $V_5$, and a minute, slurred R wave was recorded in $V_6$. A QS deflection as far to the left as precordial Positions 4 and 5 pointed toward an infarct of the anterior and anterolateral wall of the left ventricle. The diagnosis would have been more certain if an initial R had been present in Leads $V_1$ and $V_2$. The electrode in these positions was in the vicinity of the right atrium, as judged by the contour of the P wave. The QS complex recorded in Leads $V_1$ and $V_2$ was compatible with extension of the infarct into the septum. There was an abnormal RS-T elevation of 3.0 mm. in Lead $V_2$ and a borderline displacement of 2.0 mm. in $V_1$, $V_3$, and $V_4$. The T wave was upright in Leads $V_1$ through $V_5$ and flattened in $V_6$. The RS-T segment showed a normal upward concavity and was thus atypical for recent myocardial infarction. It is noteworthy that both the QS and the RS-T and T-wave complexes in the first four precordial leads corresponded closely in contour with the reciprocal of the pattern in Lead $aV_F$. Two subsequent tracings during the next five days showed no significant change in the contour of the RS-T segment and T wave. From the unipolar limb leads, the heart appeared to be in vertical position. The standard leads were abnormal, but were not diagnostic of recent myocardial infarction.

*Pathologic Findings.*—The heart weighed 429 grams and exhibited a large, transmural anterior infarct approximately one week in duration, which extended into the lateral wall of the apex and into the apical three-fourths of the interventricular septum in a manner almost identical with that in Case 34 (Fig. 8). The transmural infarction of the anterolateral portion of the apex was apparently responsible for the QS complex in Lead $V_5$ and the transmural infarct of the apical three-fourths of the anteroseptal wall and adjoining interventricular septum accounted for the QS complex in the first four precordial leads. The preservation of the normal upward concavity of the RS-T segment was an uncommon finding in recent anterior infarction and the absence of serial changes in the RS-T and T-wave complex over a period of six days was most extra-

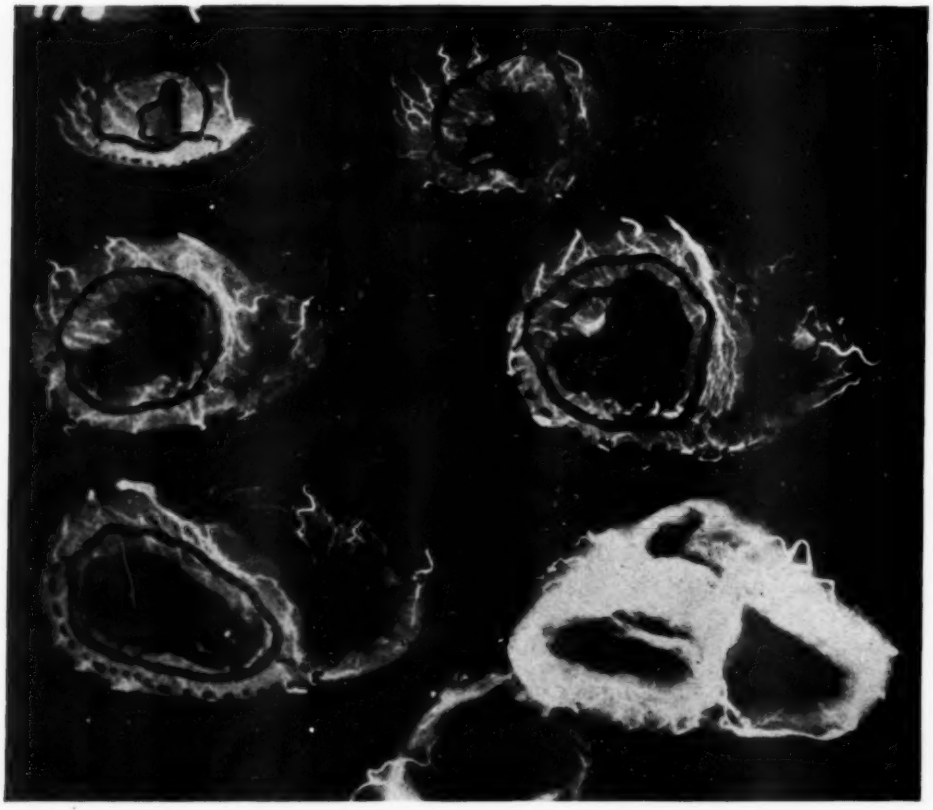

Fig. 10.—Roentgenogram of the injected heart of Case 38, showing old posterior infarction outlined in dotted lines and recent subendocardial infarction outlined in solid lines.

ordinary. These unusual features were probably referable to the complete infarction of the anterior wall found on microscopic examination. A completely destroyed anterior wall should produce no electromotive force and should merely serve as a conducting window for the precordial transmission of potentials referred to the cavity during both activation and repolarization of the intact posterior wall.[4-14] Activation of the hypertrophied but uninfarcted posterior diaphragmatic wall resulted in the transmission of positive potentials to the left leg, recorded as a tall R in $aV_F$, and in the simultaneous transmission of opposite negative potentials to the cavity. The registration of a QS complex in Leads $V_1$ through $V_4$, which was almost an exact reciprocal of the R in $aV_F$, suggested that the QS deflection represented cavity potentials, unmodified in their transmission through a transmurally infarcted septum and anterior wall. Repolarization

of the hypertrophied posterior diaphragmatic wall was manifested by a depressed, upwardly convex RS-T segment and inverted T wave in $aV_F$ and should have produced an opposite pattern in a cavity lead. The repeated registration in the first four precordial leads of an elevated, upwardly concave RS-T segment and upright T wave, which constituted almost an exact reciprocal of the pattern in $aV_F$, suggested that the RS-T and T-wave complex in these leads represented cavity potentials derived from repolarization of the posterior wall and unmodified in their transmission through a dead anterior wall. In comparison of the electrocardiogram in Case 24 with that in the present case, a striking similarity will be noted in the QS deflections of the first five precordial leads, but a significant difference will be found in the RS-T segments. The abnormally elevated RS-T junctions and convex RS-T segments in Leads $V_1$ through $V_4$ in Case 24 simulated those produced by injury localized to the subepicardial layer and indicated the presence of muscle in this layer that was injured, but not dead.

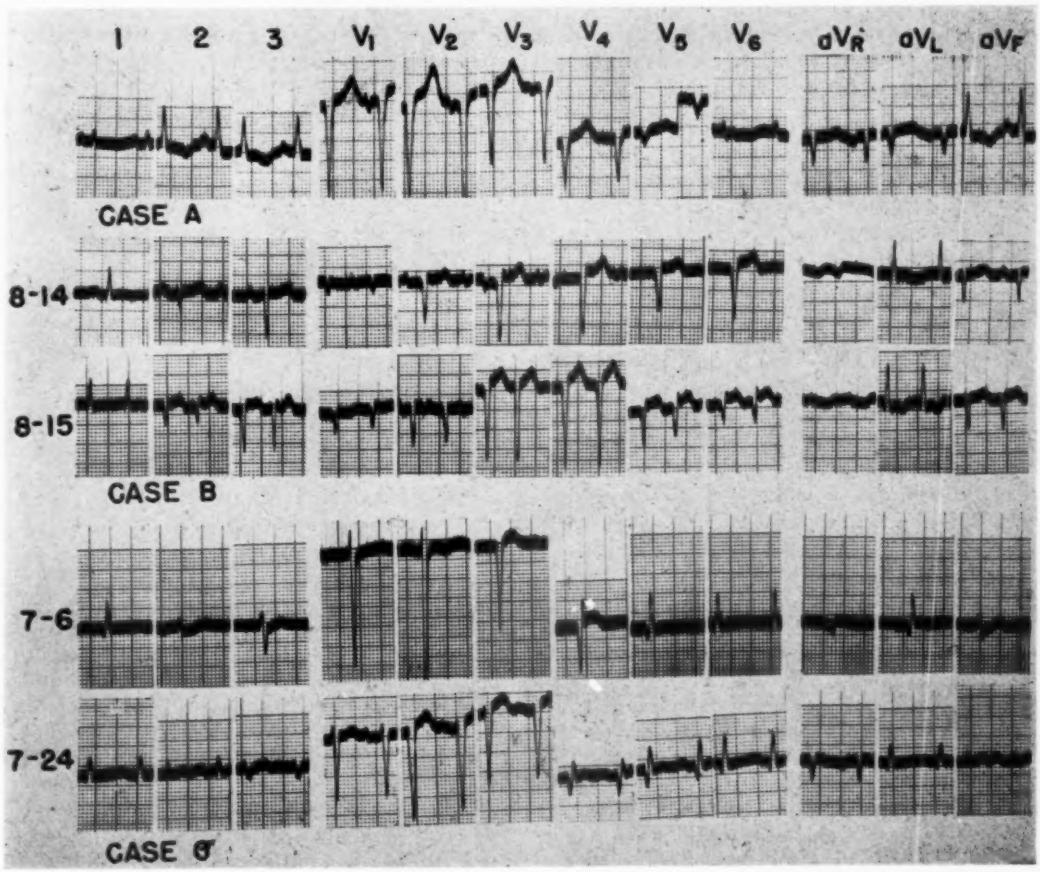


Fig. 11.—Recent anterolateral infarction. *A*, Case 39; *B*, Case 41; *C*, Case 42.

CASE 40.—A man, 58 years of age, was in good health until one month before hospital admission, when typical symptoms of diabetes mellitus developed. Two weeks before entry he was suddenly seized with sharp precordial pain and dyspnea, lasting four hours, and four days prior to entry he had a second similar attack. The patient was mentally confused throughout his entire hospital stay and died suddenly on the seventeenth day.

*Electrocardiographic Findings.*—Electrocardiograms were obtained on the third, fifth, and seventh hospital days, but are not reproduced because of their close resemblance to those in Case 39 (Fig. 11,*A*). Leads $V_1$ through $V_4$ displayed a QS complex, a 2.0 mm. elevation of the RS-T junction, an upwardly concave RS-T segment, and upright T wave similar to the corresponding leads in Case 39. In Lead $V_5$ there was a notched QS complex, an isoelectric RS-T, and low upright T wave. The QRS pattern in Leads $V_6$, $aV_L$, and $aV_F$ was almost identical with that in Case 39. Lead I displayed a small QS complex, rather than an R wave, because of the fact that the negative potentials referred to the left arm were of greater magnitude than those referred to the right arm. Furthermore, no significant change in the QRS-T complex of any precordial or limb lead was demonstrable in the electrocardiograms taken on the fifth and seventh hospital days. Unfortunately, no further tracings were obtained during the last ten days in the hospital. The QS complex in Leads $V_1$ through $V_5$ pointed strongly toward a large infarct of the anterior and anterolateral walls and the preservation of the normal upward concavity of the RS-T segment and the lack of serial changes in the RS-T and T-wave complex over a five-day period suggested either that the infarct was old and healed or that it was recent and had destroyed the entire anterior wall, as in the previous case.

*Pathologic Findings.*—The heart weighed 516 grams and exhibited an organizing anterior infarct almost identical in size and position with that in Case 39. On microscopic examination the infarct was judged to be about three weeks of age and was found to involve the entire thickness of the anterior wall and septum. Thus, the complete transmural infarction of the anteroseptal portion of the left ventricle and interventricular septum could account for the QS complex, the upwardly concave RS-T segment, and absence of serial change in the RST-T complex of Leads $V_1$ through $V_4$.

CASE 41.—A woman, 74 years of age was well until a fortnight before admission to the hospital, when she had an attack of severe epigastric and retrosternal oppression which lasted twenty-four hours. The patient was admitted in severe congestive heart failure and died three days later.

*Electrocardiographic Findings.*—Electrocardiograms obtained on August 14, five hours after admission and before administration of cardiac glycosides, and on the following day, after administration of 0.4 Gm. of digitalis, are reproduced in Fig. 11,*B*. The QS complex found in all precordial leads on August 14 was strongly suggestive of a very large anterior and anterolateral infarct, but additional leads to the right of $V_1$ and to the left of $V_6$ would have been desirable to delineate the lesion. The elevated RS-T junction, upwardly concave RS-T segment, and erect T waves in Leads $V_2$ through $V_6$ were compatible with complete transmural infarction, as brought out in the discussion of Case 39. The pattern in the precordial leads was an approximate reciprocal of the prominent R, depressed, upwardly convex RS-T, and inverted T of $aV_L$. It was believed that the pattern in $aV_L$ was derived from an uninfarcted basal portion of the lateral wall. The minute R and prominent S of $aV_F$ were apparently transmitted from the posterior inferior surface of the right ventricle, as a result of horizontal position of the heart. The standard leads showed marked left axis deviation of a type compatible with left ventricular hypertrophy, but were not diagnostic of infarction. The tracing taken the following day showed auricular fibrillation with a ventricular rate of approximately 165. No significant change had occurred in the QRS complex or T wave. Slight upward concavity was still detectable in the RS-T segments of Leads $V_3$ and $V_4$, but those of $V_5$ and $V_6$ appeared straightened, perhaps because of a combination of digitalis and rapid heart rate. A third tracing taken on August 16, but not reproduced, showed resumption of sinus rhythm and return to a QRS-T pattern similar to that of the first tracing.

*Pathologic Findings.*—The heart weighed 422 grams and exhibited an organizing infarct corresponding to the area of avascularity in the roentgenogram (Fig. 12). The entire circumference of the left ventricle in the apical segment and the anteroseptal wall and septum in the second and third segments showed complete infarction of their entire thickness. In the second segment, the infarct extended into the subendocardial one-fourth of the lateral and posterior walls, and in the fourth segment it involved the subendocardial half of the anteroseptal wall. The remainder of the heart was intact and the infarct demonstrated at autopsy was, therefore, not as

large as that predicted from the electrocardiogram. The QS deflection and the upwardly concave RS-T segment and erect T in the first four or five precordial leads were apparently a manifestation of the complete transmural infarction of the apical three-fifths of the septum and anterior wall, and the pattern in $V_6$ may have been derived from this or perhaps from the circumscribed infarct in the lateral aspect of the apical segment. This case exemplifies the tendency to overestimate the size of the infarct from electrocardiographic interpretation when the heart and thorax are relatively small. An infarct of given size tends to produce Q-wave abnormalities in a greater number of precordial leads when the heart and thoracic cage are small than when large.

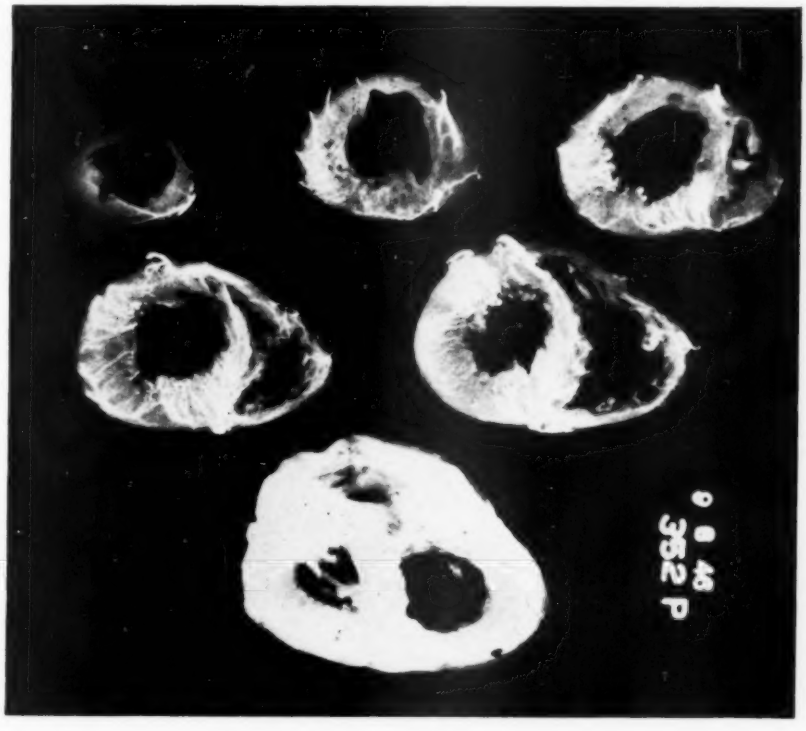


Fig. 12.—Roentgenogram of the injected heart of Case 41, showing anterolateral infarct demarcated by its avascularity.

CASE 42.—A man, 48 years of age, had had hypertension for twelve years, increasing exertional dyspnea for one year, and paroxysmal nocturnal dyspnea for three months, but denied chest pain. He was admitted to the hospital in marked congestive heart failure, remained decompensated in spite of intensive therapy, and died in circulatory collapse on July 26.

*Electrocardiographic Findings.*—Electrocardiograms obtained on July 6 and 24 are reproduced in Fig. 11,*C*. The first tracing, taken after the administration of a total of 6.0 mg. of Cedilanid parenterally during the preceding four days, showed auricular fibrillation with ventricular rate averaging 90 to 100 per minute. From the presence of a QS deflection in Lead $V_3$, a QR complex with an abnormally deep Q in $V_4$ and with an abnormally broad Q in $V_5$ and $aV_L$, in conjunction with a normal initial R in $V_1$ and $V_2$, a diagnosis was made of anteroseptal infarction, extending into the subendocardial portion of the aterolateral wall of the apex. Leads $V_3$ and $V_4$ displayed an abnormally elevated RS-T junction and upwardly convex RS-T segment and monophasic, upright T wave, which at first glance was suggestive of recent infarction; however, the marked shortening of the QT interval suggested that the RS-T and T-wave changes were due to the ex-

cessive doses of Cedilanid. This was supported by the resemblance of the RS-T and T-wave pattern in $V_3$ and $V_4$ to that produced by the administration of toxic doses of digitalis to cats.[15] On the other hand, the lack of evidence of marked digitalis effects in other leads left the interpretation in doubt. Cedilanid was discontinued on July 6 and daily doses of 1 cat unit of Digalen were given thereafter. In the tracing of July 24 the Q waves in Leads $V_5$ and $V_6$ had increased significantly in relation to the succeeding R. This suggested extension of the infarct farther into the subendocardial portion of the lateral aspect of the apex during the interim. The T waves in these leads were still flattened and were not characteristic of infarction. However, the former dome-shaped RS-T segment in Lead $V_3$ was replaced by an upwardly concave RS-T segment, and the Q-T interval had lengthened despite the increase in heart rate to 125 with restoration of sinus rhythm. This change was in keeping with decrease in digitalis effect and thus indirectly supported the premise that the former changes were due, at least in part, to the toxic effects of digitalis.

*Pathologic Findings.*—The heart weighed 523 grams and showed a large anterior infarct similar in location to that in Case 29 (Fig. 6), except for involvement of the subendocardial half of the entire lateral wall in the second segment as well as in the apical segment. The infarct of the apical two-thirds of the anteroseptal aspect of the left ventricle was confined largely to the subendocardial one-half of the wall and was judged to be at least two months of age, but showed areas of recent activity, which were probably secondary to the terminal shock. It would thus appear that the anteroseptal infarct had occurred at least one month prior to the tracing of July 6, and it is therefore probable that the RS-T and T-wave pattern in Leads $V_3$ and $V_4$ of this tracing was due largely to the excessive doses of Cedilanid. The infarct which involved the subendocardial one-half of the lateral aspect of the left ventricle in the apical two segments was judged to be approximately one week in duration and thus represented an extension during hospitalization, as was suggested by the increased depth of the Q waves in Leads $V_5$ and $V_6$.

CASE 43.—A man, 45 years of age, gave a history of an attack of prolonged retrosternal pain six months previously, from which he made a complete recovery. He had a second similar attack one month before hospitalization, followed by repeated paroxysms of nocturnal dyspnea. He was admitted to the hospital in acute pulmonary edema and became compensated during a four-day course of Cedilanid. He had no further episodes of thoracic pain and died from recurrent congestive failure five months later.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the twenty-second hospital day, eighteen days after the discontinuance of Cedilanid, is reproduced in Fig. 13,*A*. The QRS interval measured 0.12 second in Leads $V_5$ and $V_6$ and only 0.08 to 0.09 second in the standard limb leads. Since the time elapsing from onset of the QRS to the beginning of the intrinsicoid deflection was 0.02 second in Lead $V_1$ over the right ventricle and 0.08 to 0.09 second in Leads $V_5$ and $V_6$ over the left ventricle, the conduction defect was located in the left ventricle. The registration of a Q wave in left ventricular leads is most unusual in left bundle branch block, but may occur when there is extensive infarction of the septum. Under these circumstances, a longer QRS interval would have been expected. On the other hand, the QR patterns of Leads $V_5$ and $V_6$ were typical of a conduction defect in the anterolateral wall of the left ventricle. The slurred Q wave of Lead $V_6$, which measured 0.04 second from onset to nadir, and the succeeding notched upstroke, which covered 0.05 second from onset to peak, pointed to a lesion, chiefly in the subendocardial layer, which caused retardation in the spread of the impulse through the wall. The descending limb of the Q wave of Leads $V_5$ and $aV_L$ exhibited a notch similar to that occurring on the ascending limb of the R of $V_6$. This caused a lengthening of the time elapsing from onset to nadir of Q wave in Leads $V_5$ and $aV_L$ to the unusually long interval of 0.06 second. The notched downstroke and subsequent precipitous upstroke in Lead $V_5$ and the steeper downstroke, but more gradual notched upstroke of $V_6$ were merely different manifestations of the same defect and were both attributable to a lesion of the subendocardial portion of the outer wall of the left ventricle. The QS pattern in Lead $V_4$ was attributed to transmural infarction of the apical portion of the anteroseptal wall, particularly in view of the 1.5 to 2 mm. initial R wave of $V_1$ and $V_2$, and the decrease to 0.5 mm. in Lead $V_3$. Since serial tracings taken over a period of five months showed no significant change in QRS or RS-T pattern, a diagnosis was made of an old infarct, involving the apical portion of the anterior and lateral walls of the left ventricle.

*Pathologic Findings.*—Autopsy disclosed an old, healed infarct, involving the apical half of the anterior and lateral wall of the left ventricle, comparable in distribution to that in Case 44 (Fig. 14), except that it extended for a short distance into the left side of the apical one-third of the septum. The lesion was characterized by dense fibrosis of the subendocardial one-half to two-thirds of the anterolateral wall with fingerlike projections to the epicardial surface. Thus, there was good correlation between the position of the anterolateral portion of the infarct as predicted from the electrocardiogram and as demonstrated at autopsy. The extension into the septum was not detected electrocardiographically.

CASE 44.—A man, 71 years of age, was struck by an automobile and was brought to the hospital in stupor with multiple rib fractures. Past history was not obtainable. Bronchopneumonia developed on the fourth day and caused death on the eighth day.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the fifth hospital day, before the administration of cardiac glycosides, is reproduced in Fig. 13,*B*. The P-R interval was at the lower limit of normal. The initial phase of the QRS in the first four precordial leads consisted of an R wave, which measured 2.0 mm. in Lead $V_1$ and 4.0 mm. in $V_2$, and fell off to 2.0 mm. $V_3$, and to 0.5 mm. in Lead $V_4$. Leads $V_5$ and $V_6$ displayed a slurred Q wave 0.02 to 0.03 second in duration and approximately 50 per cent of the amplitude of the succeeding R. This was taken as evidence of an infarct involving the subendocardial portion of the anterolateral wall of the left ventricle. The dome-shaped RS-T segments and very slightly inverted T waves in these leads were suggestive of organization, but might have represented a fixed residue. More striking changes in the T wave were found in the first three precordial leads and consisted of sharp inversion associated with an elevated RS-T junction in $V_1$ and an approximately isoelectric take-off in the other leads. The question arose as to whether these changes were due to acute right ventricular dilatation or a recent anteroseptal infarction. The sharp downstroke in the P waves of Leads $V_1$ and $V_2$ suggested that the electrode was in the vicinity of the right atrium. The registration of a normal initial R in Leads $V_1$ and $V_2$ (which were considerably to the right of the septum) and the deeper inversion of the T waves in these leads than in Leads $V_3$ and $V_4$ (which were nearer to the septum) were strongly against recent anteroseptal infarction, but were in favor of acute right ventricular dilatation. The prominent late R wave in $aV_R$ was probably transmitted from the posterobasal aspect of the left ventricle and suggested backward displacement of the apex. The prominent Q wave of $aV_L$ was almost cancelled out in Lead I because of simultaneous initial negativity of the right arm. Consequently, the standard leads were not diagnostic of infarction.

*Pathologic Findings.*—The heart weighed 512 grams and exhibited an aneurysm of the anterolateral aspect of the left apex due to an old, completely healed infarct of the subendocardial three-fourths of the wall, as outlined in Fig. 14. There was satisfactory correlation between the infarct of the anterolateral wall of the apex and the abnormal QR pattern in Leads $V_5$, $V_6$, and $aV_L$. The abnormal RS pattern in $V_2$ and $V_4$ did not accurately portray the continuation of the infarct subendocardially into the anteroseptal wall, which should have produced a QS and QR deflection in these leads. The abnormally small R may have been derived from undetected islands of preserved muscle in the dense subendocardial infarct. A more likely alternative explanation was suggested by the backward rotation of the apex, deduced from the pattern in Lead $aV_R$. This may have carried the apex far enough away from the precordium to have hindred transmission of its potential variations to precordial Position 4 and thus may have indirectly favored reference of positive potentials from points to the right of or above the apical infarct. A patchy fibrosis was found in the subendocardial portion of the posterior wall, as represented by the stippling, but was not detected electrocardiographically. Autopsy also disclosed a moderate acute right ventricular dilatation, secondary to the bronchopneumonia. Although this seemed a better explanation for the inverted T waves in Leads $V_1$, $V_2$, and $V_3$ than the old, healed anteroseptal infarct, it was not altogether satisfactory, since greater right ventricular dilatation has been observed in association with erect T waves in these leads.

CASE 45.—A man, 56 years of age, gave a six-year history of angina pectoris. He had had two previous bouts of prolonged retrosternal pain, complicated by congestive failure, and was admitted to the hospital following a third similar attack. Death occurred on the thirtieth hospital day.

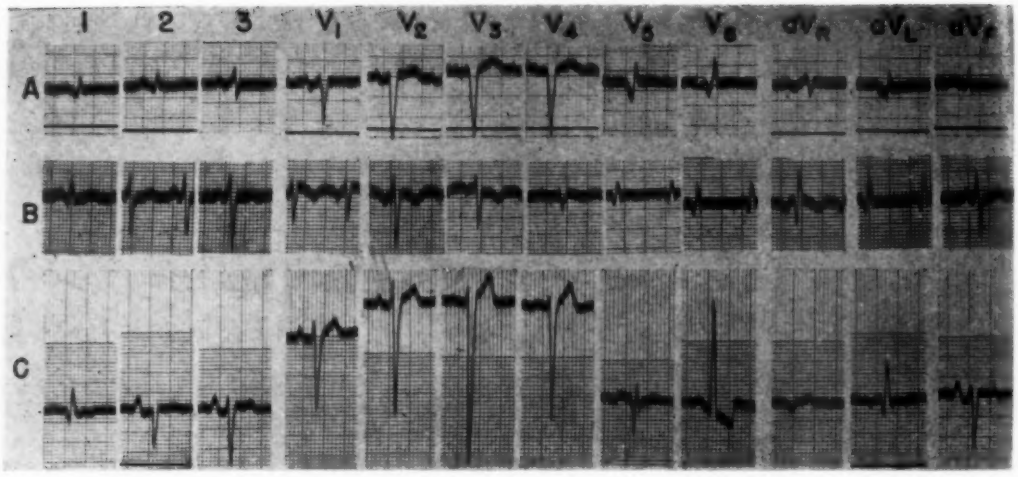


Fig. 13.—Old anterolateral infarction. *A*, Case 43; *B*, Case 44; *C*, Case 45.

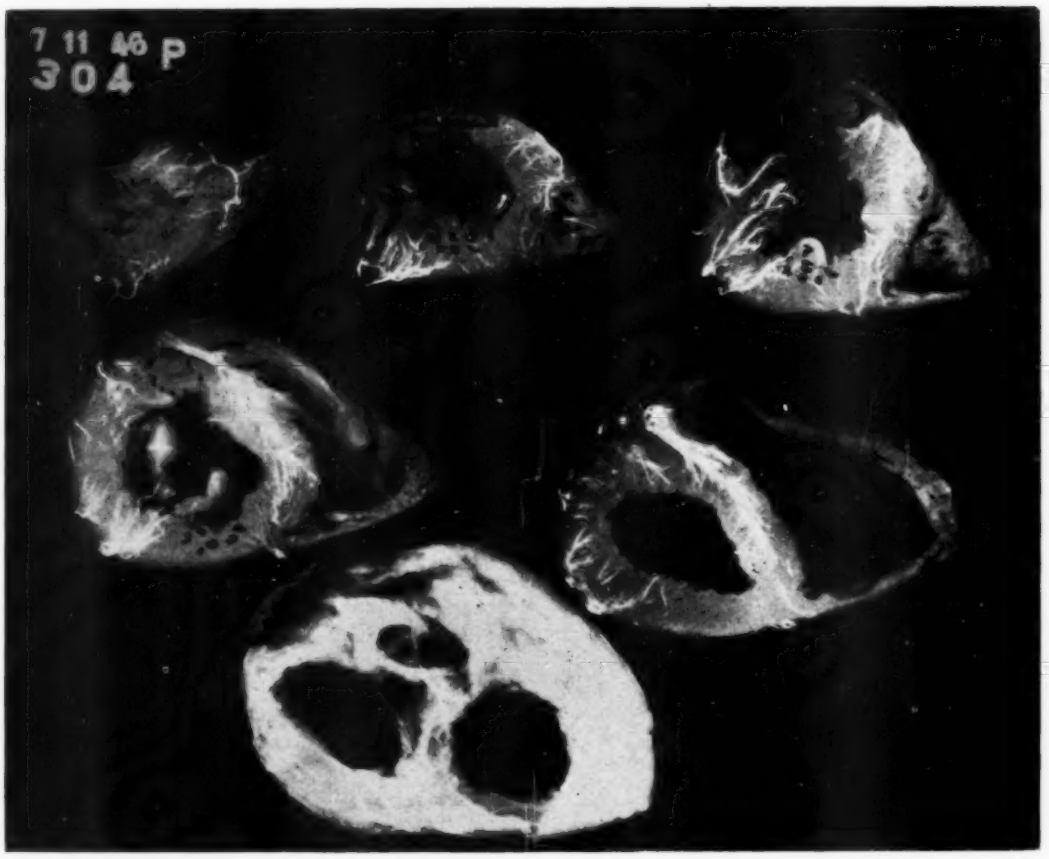


Fig. 14.—Roentgenogram of injected heart of Case 44.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the seventh hospital day, while the patient was receiving maintenance doses of digitalis, is reproduced in Fig. 13,*C*. The initial R showed the expected increase in amplitude as the electrode was moved from Position 1 to 2 and then a progressive paradoxical decrease at Positions 3 and 4. In view of these findings, the deep Q in Lead $V_5$ was diagnostic of infarction of the anterolateral aspect of the apex. The minute Q and tall succeeding R wave in Lead $V_6$ were compatible with left ventricular hypertrophy and were not diagnostic of infarction. The contour of the depressed RS-T segment in this lead was typical of digitalis effect. The findings in Lead $aV_R$ suggested backward rotation of the apex and when considered along with the inverted P wave in $aV_L$, suggested that the abnormal QR pattern in $aV_L$ was more likely transmitted from the posterolateral than from the anterolateral wall of the left ventricle. The infarct was considered old and healed because of the absence of significant changes in serial electrocardiograms. Standard Lead I showed an abnormal QR typical of anterolateral infarction. The initial R wave of Lead $aV_F$ was not carried over into Lead II because of cancellation by a simultaneous positive potential of equal magnitude referred to the right arm, as will be appreciated by comparison of the initial upward deflections of $aV_R$ and $aV_F$.

*Pathologic Findings.*—The heart weighed 504 grams as a result of left ventricular hypertrophy. There was an old, patchy infarct of the anteroseptal and anterolateral aspect of the apex, occupying essentially the same position in the first two segments as that in Case 21 (Fig. 2), but smaller and more sparse in the third segment. This was apparently responsible for the decreasing R wave in Leads $V_3$ and $V_4$ and for the abnormal Q wave in $V_5$. In addition, there was a separate healed infarct of the apical two-thirds of the posterolateral aspect of the left ventricle. Because of the backward rotation of the heart, it is possible that the abnormal QR pattern in $aV_L$ was transmitted from this rather than from the anterolateral infarct. No evidence of the posterior portion of this infarct was elicited in $aV_F$, apparently because the potential variations of the right ventricle were referred to the left leg.

CASE 46.—A man, 57 years of age, who had had transient retrosternal oppression and dyspnea on exertion since January, 1945, was first admitted to the hospital on March 25, 1945, in severe congestive failure precipitated by a prolonged attack of retrosternal constriction. Compensation was restored with the aid of digitalization. The patient was fairly comfortable until March, 1947, when angina pectoris and paroxysmal nocturnal dyspnea recurred, followed by congestive failure in May. At this time, signs of an apical cardiac aneurysm were demonstrated by physical and roentgen examination. Compensation was again restored, but cardiac failure recurred after discharge, resulting in death the following month.

*Electrocardiographic Findings.*—Electrocardiograms which were obtained on April 11, 1945, while the patient was on maintenance doses of digitalis, and exactly two years later, long after the discontinuance of digitalis, are reproduced in Fig. 15,*A*. In the first three precordial leads taken on April 11, 1945, there was an initial upright deflection which was similar in amplitude in Leads $V_1$ and $V_2$, but significantly smaller in $V_3$. The central zonal pattern of Leads $V_4$ and $V_5$ was representative of a transmural infarct of the anterolateral wall of the apex, and the marginal zonal pattern of $V_6$ was taken as evidence of extension of the infarct farther into the lateral wall. Although the ratio of Q to R in Lead $aV_L$ was only 25 per cent, the Q wave in this lead was definitely abnormal because of its coarse notching and broadening and was also indicative of infarction of the subendocardial portion of the lateral wall. The RS-T displacement in Leads $V_4$, $V_5$, and $V_6$ and inversion of the T wave in $V_6$ and $aV_L$ were referable to the stage of organization. Lead I also showed typical signs of anterolateral infarction. In the tracing made two years later, the main change consisted in a lengthening of the QRS interval from 0.10 second to 0.15 second and the concomitant development of coarse slurring or notching of the QRS in all leads. From a study of the standard leads, it would appear that left bundle branch block had developed. However, the presence of an initial downward deflection in precordial leads over the left ventricle was strongly against this type of conduction defect, since the activation of the septum from right to left, necessitated by left bundle branch block, causes early positivity of the left ventricular cavity and hence an initial upright deflection in all leads facing the left ventricle. The registration of an abnormal Q wave in leads over an infarct of the anterolateral wall of the left ventricle is

possible in the presence of left bundle branch block if the entire septum or the major portion of it is destroyed by infarction. Under these circumstances, early negativity of the right ventricular cavity (resulting from activation of the outer wall of the right ventricle) might be transmitted through the inert septum to the left ventricular cavity, thus initiating the Q wave in left ventricular leads. Increasing negativity of the left ventricular cavity would be expected as the impulse reaches and activates uninfarcted portions of the outer wall of the left ventricle, thereby adding to the Q wave recorded through leads overlying the infarct. Although the combination of left bundle branch block and complete infarction of the septum could not be positively excluded,

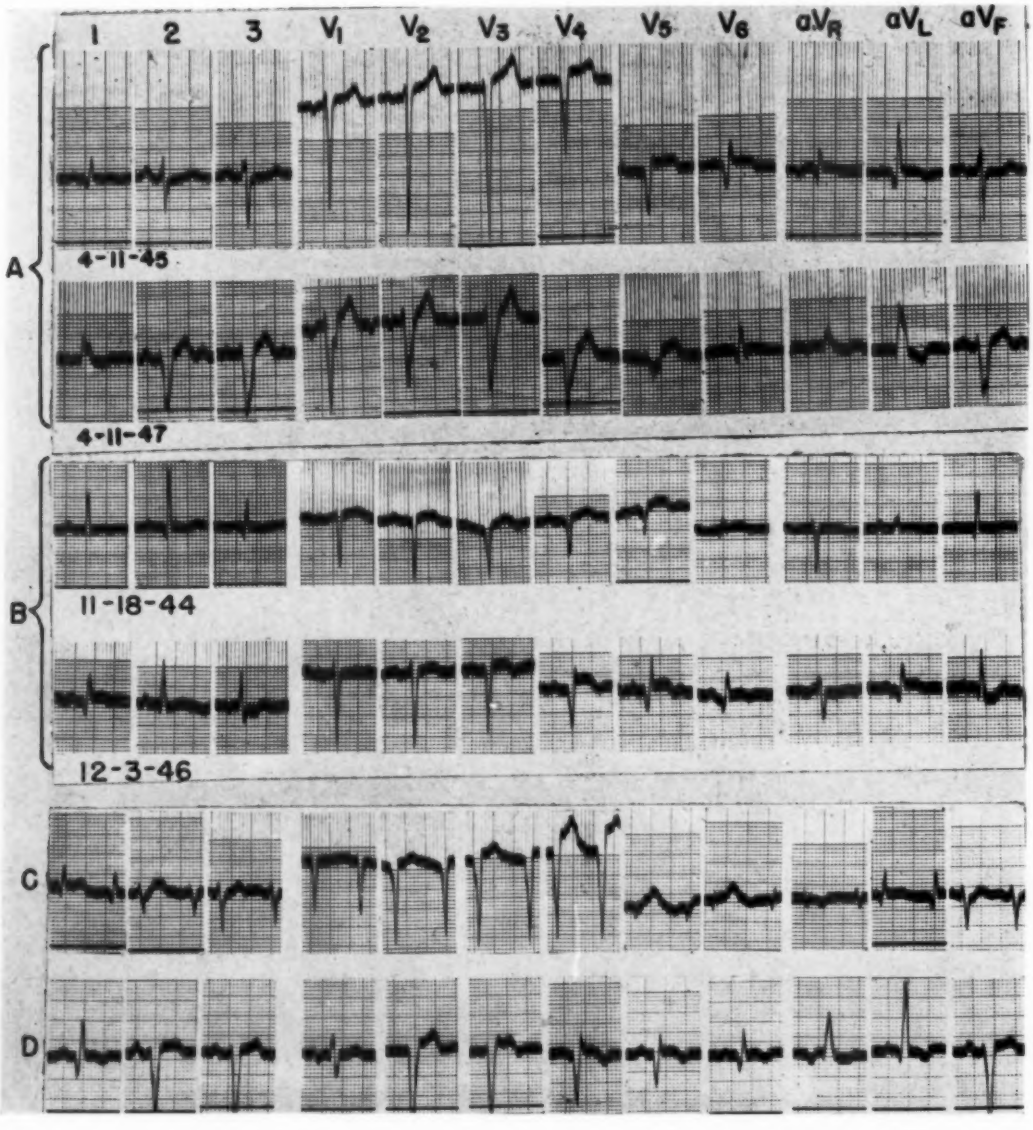


Fig. 15.—Old anterolateral infarction with ventricular aneurysm. *A*, Case 46; *B*, Case 47; *C*, Case 48; *D*, Case 50.

the prominent Q and late intrinsicoid deflection in Leads $V_6$ and $aV_L$ were more likely an expression of a conduction defect in the lateral wall of the left ventricle. Because of initial negativity of both the right and left arm, the first portion of $QRS_1$ was isoelectric and the first phase registered in this lead was upright. An initial R was still present in Leads $V_1$, $V_2$, and $V_3$ and the ratio of amplitudes of R and S waves in these leads did not differ significantly from those observed two years previously. Leads $V_4$ and $V_5$ still displayed a QS complex, an elevated RS-T junction, and monophasic, upright T wave. The T wave in Lead $V_5$ was an exact reciprocal of that in $aV_L$ and, like the QS, was representative of cavity potentials transmitted without modification through a completely infarcted anterolateral apical wall. The S wave, which had been added to the QR of Lead $V_6$, merely indicated that the electrode was not over the last portion of the left ventricle to become activated. The absence of an S wave in $aV_L$ suggested that this lead reflected the potential variations of a more lateral portion of the left ventricle. The development of the conduction defect was in keeping with fibrosis secondary to the healing of an infarct of the subendocardial portion of the lateral wall, and the lack of any significant change in QRS relationships was against extension of the infarct during the two years intervening between the two tracings. Furthermore, several additional electrocardiograms were obtained during the last three months of his life and showed no significant changes in QRS-T, indicating that the tracing of April 11, 1947, was representative of a fixed pattern, as the result of an old infarct of the anterior and lateral aspects of the apex. A high precordial lead taken in the mid-clavicular line at the level of the junction of third intercostal space and sternum revealed a small, M-shaped QRS, and high axillary leads at the same horizontal level resembled Lead $aV_L$. The disappearance of diagnostic patterns in high leads suggested that the infarct did not involve the basal portion of the anterolateral wall.

*Pathologic Findings.*—The heart weighed 744 grams and exhibited a large, healed infarct, which caused complete fibrous replacement of the entire circumference of the two apical segments of the left ventricle, as is evident in Fig. 16. The infarct was manifested by dense fibrosis of the subendocardial one-half to three-fourths of the anterolateral wall in the next three segments, corresponding to the areas of avascularity, but spared islands of muscle, chiefly in the subepicardial layer. The infarcted area was the site of a large aneurysm, the apical portion of which was filled with a mural thrombus. The QS complexes, RS-T displacement, and upright T waves in Leads $V_4$ and $V_5$ were well correlated with the aneurysm of the anterolateral aspect of the apex. The infarct had converted the septum into a fibrous membrane in the two apical segments and extended into the anterior portion of the left side of the septum in the next three segments, but did not involve the basal one-half of the septum. The limitation of the septal infarction to the apical one-half was strongly against left bundle branch block as a cause of the conduction defect, since the activation of the intact basal one-half from right to left (necessitated by left bundle branch block) should have produced an initial R wave in all leads over the left ventricle. The abnormal Q and very broad, slurred R in Leads $V_6$ and $aV_L$ could be accounted for by the interspersing of dense patches of fibrosis and islands of intact myocardium in the lateral wall of the left ventricle above the apex. A separate healed intramural infarct situated in the basal one-half of the lateral wall, labelled as *B* in Fig. 16, may have contributed to the abnormalities in $V_6$ and $aV_L$. The involvement of the posterior wall was not evident electrocardiographically, probably because of the horizontal position of the heart.

CASE 47.—A woman, 80 years of age, was first hospitalized in March, 1941, because of recent anterior infarct, diagnosed by serial electrocardiograms. Convalescence was uneventful and her heart was fairly well compensated when she was next admitted in November, 1944, because of esophageal diverticulum. She was readmitted moribund in congestive heart failure on Dec. 2, 1946, and died forty-one hours later.

*Electrocardiographic Findings.*—Electrocardiograms obtained on Nov. 18, 1944, when she was not under the influence of cardiac glycosides, and on Dec. 3, 1946, after the administration of 0.8 mg. of Cedilanid, are reproduced in Fig. 15,*B*. In Lead $V_1$ of the first tracing there was a distinct initial R, and in Leads $V_2$ through $V_5$ there was a QS complex with a notch (R equivalent) near the base of the descending limb of the Q wave. These findings pointed to a large infarct of the anteroseptal and anterolateral wall of the left ventricle, which extended subendocardially into the

lateral wall, as shown by the abnormal QR complex in $V_6$. In Lead $aV_F$ there was a 2.0 mm. Q wave, which was 25 per cent of the succeeding R. The fact that the borderline Q to R ratio was accompanied by slurring of the ascending limb of the R was interpreted as evidence of extension of the infarct into the subendocardial portion of the posteroapical wall. The RS-T junction was slightly elevated and the T wave upright in all precordial leads. Although the domelike contour in $V_6$ was suggestive of recent infarct, a fixed residue from the old infarct sustained three and one-half years previously appeared more likely. The standard leads were suggestive of posterior infarction, but gave no positive indication of the large anterolateral infarct. The tracing of Dec. 3,

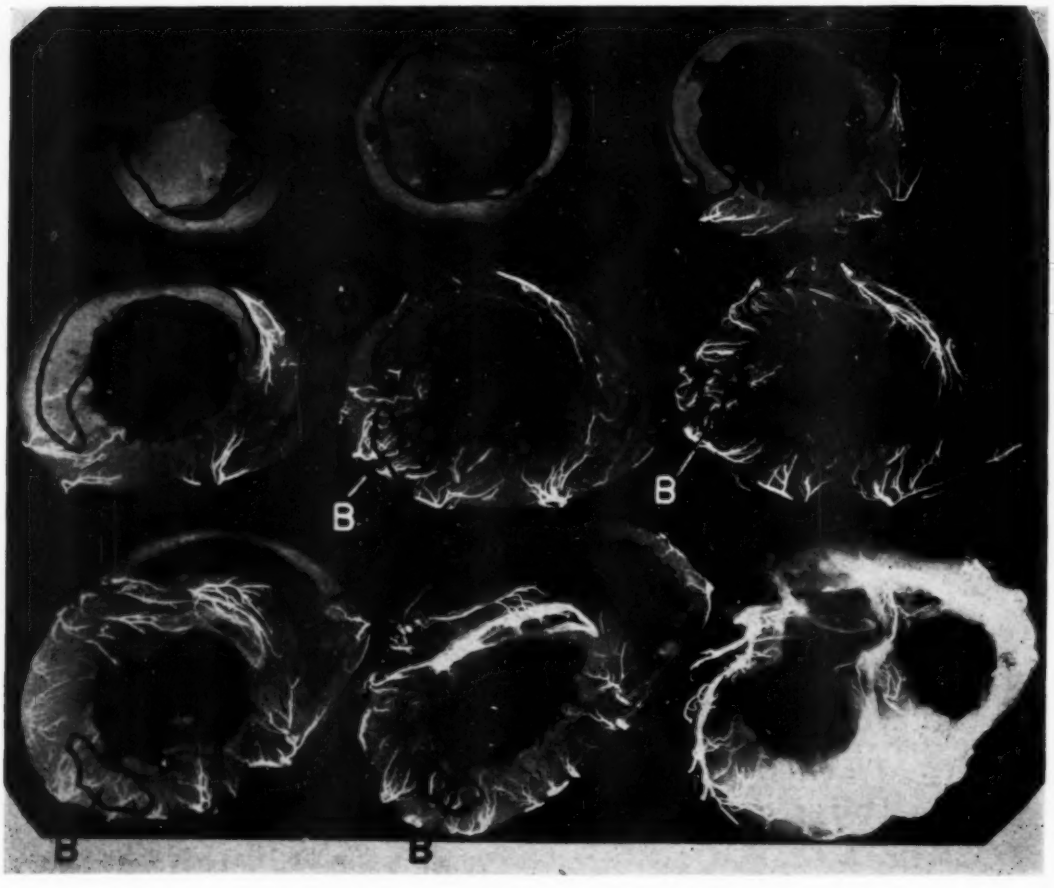


Fig. 16.—Roentgenogram of the injected heart of Case 46.

1946, showed a distinct initial R in the first two precordial leads, slightly larger in $V_1$ than in $V_2$. In view of these findings, the QS pattern in $V_3$ was significant of a central zone of transmural infarction. Leads $V_4$, $V_5$, $V_6$, and $aV_L$ displayed a QR complex with abnormally deep and prolonged Q wave. Furthermore, the ascending limb of the R wave in Leads $V_5$ and $V_6$ was slurred and the time interval from its onset to peak was prolonged to 0.05 second. These findings were typical of the marginal zone of subendocardial infarction, extending into the anterolateral and lateral wall of the left apex. The appearance of a Q in Lead $aV_L$ together with increased RS-T displacement in Leads $V_4$, $V_5$, $V_6$, and $aV_L$ and the classical domelike contour of the RS-T segment suggested that the old infarct had recently extended farther into the anterolateral and

lateral wall of the left ventricle. This diagnosis was supported by the reciprocal depression of the RS-T segment in Leads $aV_F$ and III. The Q wave of Lead $aV_L$ carried over into standard Lead I, producing a pattern typical of anterolateral infarction. The QR complex in Lead $aV_F$ was much like that in the tracing made two years previously. However, the Q wave was cancelled from standard Lead III, because the left arm was more negative than the left leg early in the course of cardiac activation (as shown by the registration of a deeper Q in $aV_L$ than in $aV_F$). The initially negative potentials of the left arm, which were recorded as a Q wave in $aV_L$, were registered as an R wave in Lead III, which fused with the upright deflection because of the subsequent positivity of the left leg. Thus, the standard leads of the final tracing were diagnostic of the anterolateral infarct, but gave no evidence of the involvement of the posterior wall.

*Pathologic Findings.*—The heart weighed 624 grams and exhibited left and secondary right ventricular hypertrophy and an aneurysmal protrusion of the apex. There was a large infarct, causing complete fibrous replacement of the apical segment of the left ventricle and involving the entire circumference in the second segment and the left side of the septum and adjoining subendocardial portion of the anteroseptal wall in the third and fourth segments. The location of the infarct was closely comparable to that in Case 46 (Fig. 16). The infarct was old and healed except in the anterolateral wall of the second segment, where there was microscopic evidence of an old subendocardial infarct and a recent organizing infarct, extending in patchy fashion through the remainder of the wall. Thus, the QS pattern in Lead $V_3$ and the abnormal QR in $V_4$, $V_5$, and $V_6$ could be correlated satisfactorily with the transmural infarction of the anteroseptal wall and the incomplete transmural infarction of the anterolateral wall of the apex. The electrocardiographic findings suggesting recent lateral extension were borne out at autopsy. The involvement of the posterior portion of the apex was probably responsible for the Q in Lead $aV_F$. On the other hand, the infarction of the septum was not detected electrocardiographically. It is probable that the R waves in Leads $V_1$ and $V_2$ were derived from activation of the hypertrophied right ventricle.

CASE 48.—A man, 62 years of age, was admitted because of left-sided Jacksonian convulsions and left hemiparesis of three weeks' duration. Past history was unobtainable. The association of a diffuse, heaving apical impulse with a faint first sound suggested ventricular aneurysm. Blood pressure was 180/130. No cardiac glycosides were given. Death occurred from pneumonia on the third hospital day.

*Electrocardiographic Findings.*—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 15,*C*. Auricular fibrillation was present. Leads $V_{3R}$ and $V_1$ displayed a minute, but distinct initial R wave 0.5 mm. in amplitude. A deep QS complex, coarsely slurred on its descending limb, was present in Leads $V_2$ through $V_4$. An abnormal W-shaped complex of low voltage was found in Lead $V_5$ and a small, but abnormal Q and a minute terminal R were registered in $V_6$. The ratio of Q to R of 33 per cent in Lead $aV_L$ together with slurring of the Q and prolongation of the upstroke of the R to 0.04 second was abnormal and consistent with a marginal zone of subendocardial infarction. Lead $V_7$, which is not reproduced, exhibited an R wave of amplitude similar to that in $aV_L$ with coarse notching at its onset in place of the Q recorded in $aV_L$. The findings in the precordial leads pointed to a very broad central zone of transmural infarction in most of the anterior wall, whereas the findings in $V_6$ and $aV_L$ were indicative of extension of the infarct subendocardially into the lateral wall. The RS-T take-off was elevated 2.0 mm. in Lead $V_3$, 5.0 mm. in $V_4$, and 1.0 mm. in $V_5$. The T wave was upright in Leads $V_2$ through $V_7$ and in $aV_L$ and the RS-T segment in these leads showed the normal upward concavity. The question arose as to whether the changes in the RS-T segment and T wave were the result of a recent, complete transmural infarction or whether they were a residue of an old, healed infarction. This question was not positively settled electrocardiographically because death occurred before a second tracing could be obtained. The abnormal Q wave in Lead $aV_L$ was carried over into Lead I, producing a pattern diagnostic of anterolateral infarction in this lead.

*Pathologic Findings.*—The heart weighed 475 grams and exhibited a large aneurysm, which occupied the apical two-thirds of the anterior wall. The wall of this aneurysm was calcified, as evident from the roentgenogram (Fig. 17), and measured only 2.0 mm. in its thinnest portions. The aneurysm was the result of an old, completely healed infarct, which extended into the lateral

wall of the two apical segments and into the septum in the four apical segments. The septal fibrosis continued into the adjoining posterior wall in the two apical segments. The broad central zonal pattern in Leads $V_2$ through $V_5$ corresponded closely with the position of the large aneurysm found at autopsy. The elevated, upward concave RS-T segments and upright T waves in Leads $V_2$ through $V_5$ were comparable to those in the corresponding leads in Cases 39, 40, and 41 and probably represented cavity potentials derived from repolarization of the hypertrophied posterior and posterolateral walls which were transmitted without modification through the aneurysm to the precordium. It is probable that esophageal leads would have shown a prominent R, depressed RS-T junction, and inverted T reciprocal to the recordings in Leads $V_2$, $V_3$, and $V_4$. Unfortunately, no record was obtained of the potential variations of the posterior wall of the left ventricle in this case, since $aV_F$ displayed an RS complex, presumably transmitted from the right ventricle, due to horizontal position.

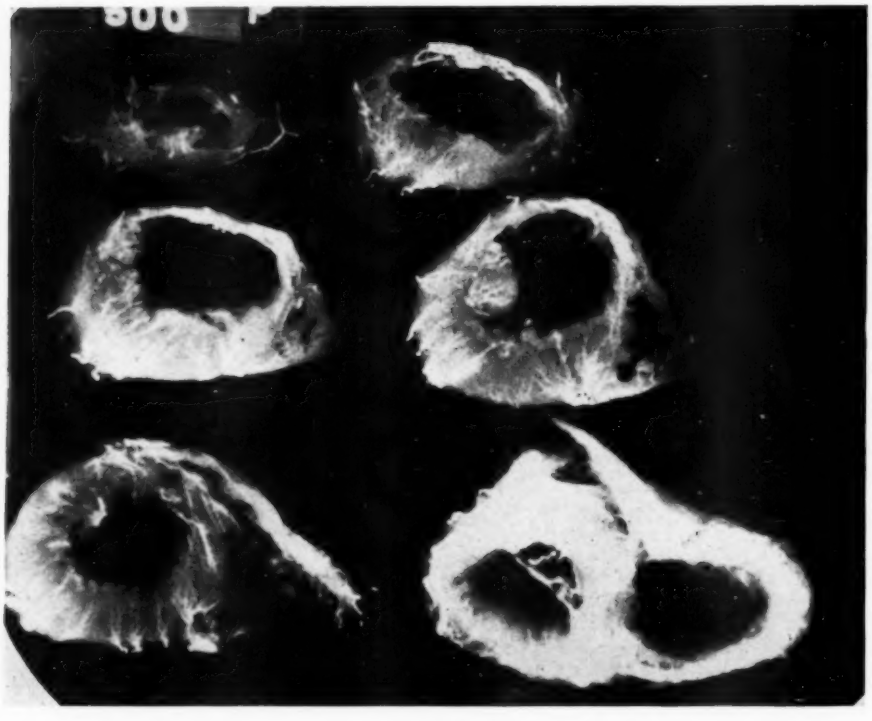

**Fig. 17.—Roentgenogram of the injected heart of Case 48, showing a large, calcified ventricular aneurysm.**

CASE 49.—A man 63 years of age, moribund, was admitted to the hospital with extreme anasarca due to congestive failure complicated by auricular fibrillation. Past history was unobtainable. Death occurred twenty-three hours later.

*Electrocardiographic Findings.*—An electrocardiogram taken after administration of 0.8 mg. of Cedilanid is not reproduced because of its close resemblance to that in Case 48 (Fig. 15,*C*). A QS pattern of central zonal type was found in the first five precordial leads and a QR pattern, like that in Lead $aV_L$, Case 48, was present in $V_6$. Lead $aV_L$ showed a minute Q, marked slurring of the ascending limb of the R, and increase of time elapsing from onset to peak of R to 0.06 second. From the QRS pattern, a diagnosis was made of a large, transmural anterior infarct, extending into the septum and continuing subendocardially into the lateral wall of the apex. The

RS-T junction was elevated 3.0 mm. in Lead $V_3$, 4.0 mm. in $V_4$, and 2.0 mm. in $V_5$. The contour of the RS-T segments and T waves in the first five precordial leads was much like that in Leads $V_3$ and $V_4$ of the tracing of July 6 in Fig. 11,*C*. The changes were ascribed to the effects of digitalis superimposed on RS-T displacement secondary to infarction. From a single tracing, a positive differentiation between a recent infarct and a fixed pattern from old infarction could not be made.

*Pathologic Findings.*—The heart weighed 714 grams as a result of marked left ventricular hypertrophy. There was an old, healed infarct of the apical three-fourths of the anterior aspect of the left ventricle, which extended into the anterior three-fourths of the septum and into the apical one-third of the lateral aspect of the left ventricle. This infarct was comparable in size and position to that in Case 48 except for failure to involve the posterior wall. Microscopic sections showed dense fibrosis, extending through the subendocardial three-fourths of the anterior and lateral walls. There was good correlation between the abnormal pattern in the precordial leads and the extensive infarction of the greater part of the anterior wall and septum and a considerable portion of the lateral wall. The RS-T abnormalities were probably referable in part to the preserved subepicardial layer of muscle and in part to the superimposed effects of digitalis.

CASE 50.—A previously healthy man, 57 years of age, was first admitted on Nov. 8, 1943, because of a paroxysm of painless nocturnal dyspnea, proved electrocardiographically to have been due to recent anterolateral infarction. On Jan. 17, 1944, he was seized with precordial pain, radiating to the left shoulder, due to an extension of his infarct farther into the lateral wall, as evidenced by an increase in the Q in Lead $V_6$ at the expense of the R. A diagnosis of apical aneurysm was later made by physical and roentgen examination. Serial electrocardiograms during the remaining twenty-seven months of his life showed no significant change in QRS pattern. He was fairly comfortable during this period except for a second severe paroxysm of nocturnal dyspnea on Oct. 29, 1945, which resulted in hospitalization, and a third attack in April, 1946, which caused death.

*Electrocardiographic Findings.*—An electrocardiogram, illustrated in Fig. 15,*D*, was obtained on Dec. 5, 1945, after stabilization of the QRS-T pattern and while the patient was taking maintenance doses of digitalis. Lead $V_1$ displayed a minute Q wave 1.0 mm. in depth, an R wave 4.0 mm. tall, and a slightly larger S wave. An initial Q preceding an RS complex is abnormal in Lead $V_1$ and may have been due to activation of the septum from right to left, as a result of septal infarction. Because of the abnormally large amplitude of R in proportion to that of S in Lead $V_1$, right ventricular hypertrophy was regarded as a possible alternative explanation for the QR pattern in Lead $V_1$. In view of the findings in Lead $V_1$, the QS complex in $V_2$ and $V_3$ was significant of central zone of infarction, occupying the anteroseptal portion of the left ventricle. The deep, broad initial downward component of the QR complex of Leads $V_4$, $V_5$, and $V_6$ pointed to infarction, extending from the endocardial surface through the greater part of the anterolateral wall of the left ventricle. Although the Q to R ratio in $aV_L$ was only about 12 per cent, the broadening of the Q wave and the slurring and prolongation of the ascending limb of the succeeding R were abnormal and also pointed to infarction of the subendocardial portion of the lateral wall. Lead $aV_R$ displayed an unusually tall, slurred R, probably derived from the posterobasal aspect of the left ventricle. The fact that this would be recorded as a downward deflection in Lead I accounts for the exceptionally deep Q wave in this lead. From the contour of the RS-T segment in Leads $V_3$ through $V_6$, one might surmise that the infarct was in the stage of organization; however, this pattern had become fixed prior to this tracing and remained so during four subsequent months of observation. Therefore, an electrocardiographic diagnosis was made of a large, transmural anteroseptal infarct, continuing into the interventricular septum and extending subendocardially into the lateral wall of the left ventricle.

*Pathologic Findings.*—The heart weighed 570 grams and exhibited a large, completely healed infarct, which involved the entire circumference of the left ventricle in the apical two segments and the anteroseptal wall and septum in the next three segments and extended for a short distance across the septum into the anterior wall of the right ventricle. The apical one-half of the anteroseptal wall of the left ventricle and the entire circumference of the apex were reduced to a thickness of 2.0 to 3.0 mm., as a result of complete fibrous replacement and aneurysm formation. The

position of the aneurysm and infarct was identical with that of Case 46 (Fig. 16), except that this lesion did not extend into the lateral wall above the second segment. The initial Q in Lead $V_1$ was most likely secondary to the extensive lesion of the septum, but might have been due in part to the small extension into the anterior wall of the right ventricle. The large aneurysm was probably responsible for the QS complex in Leads $V_2$ and $V_3$ and should have been manifested by a QS complex in $V_4$ and $V_5$ as well. The source of the late R waves in Leads $V_4$ and $V_5$ is obscure. This case also constitutes another example of cardiac aneurysm with fixation of the RS-T segment and T waves in a pattern resembling that encountered during the process of organization of a recent infarct.

## COMMENT

*Correlation Between the Leads Exhibiting QRS Abnormalities and the Location of the Lesions of the Anterior and Lateral Walls at Autopsy.*—This has been discussed in detail in each individual case report, but remains for summary. When the infarct is confined to the anteroseptal portion of the free wall of the left ventricle, abnormal QS or QR complexes are limited to one or more of the first four precordial leads.[12] When an anterior infarct continues into the lateral aspect of the apex, diagnostic QRS abnormalities are found not only in one or more of the first four precordial leads, but also in Leads $V_5$, $V_6$, and/or $aV_L$.

The findings in the first four precordial leads are, in general, comparable with those produced by an infarct limited to the anteroseptal wall of the left ventricle. An abnormal initial downward deflection in right ventricular Leads $V_1$ and $V_2$ may occur as a manifestation of extension of the infarct into the septum. An abnormal QS in Lead $V_2$ was also observed in association with an infarct involving the apical one-half of the anterior wall, but not extending into the septum, as in Case 28. The lesion of the anterior wall was characteristically manifested by QRS abnormalities in Leads $V_3$ and $V_4$. The incidence of a QS in both $V_3$ and $V_4$ was distinctly greater in this series than in the group of infarcts confined to the anteroseptal wall of the left ventricle. A QS deflection was found in both Leads $V_3$ and $V_4$ in association with infarction limited to the apical one-third, as well as with much more extensive lesions. A positive distinction between infarcts confined to the apical one-third and those involving the apical two-thirds or more of the anterior wall could not be made from the six customary precordial leads. An infarct of given size tended to produce QRS abnormalities in a greater number of leads when thorax and heart were small than when large. Hence, there was a tendency to overestimate the size of infarcts in persons with narrow chests and to underestimate the size in persons with broad chests.

The QRS pattern in Leads $V_5$, $V_6$, and $aV_L$ served to differentiate an anterior infarct extending into the lateral aspect of the apex from those limited to the septal wall. The findings in these leads have been correlated with those at autopsy in fifty-seven cases exhibiting a large anterior infarct extending into the apical one-third or more of the lateral wall (Cases 20 through 54, 56 through 59, 61, 62, 64 through 66, 69, 71, 72, 74, 77 through 80, 82, 96, and 151 through 153). An abnormal QS or QR complex was found in all three leads in twenty-seven cases, in Lead $V_5$ and in either $V_6$ or $aV_L$ in fifteen cases, in $V_5$ alone in eight, and in $aV_L$ alone in two. In several of the cases where diagnostic QRS abnormalities were present in only one or two of the three leads, borderline findings were

obtained in the remaining leads. There was no direct relation between the number of leads showing diagnostic QRS abnormalities and the extent of the involvement of the lateral wall at autopsy, since there were a number of cases in which an abnormal QR or QS pattern was found in all three leads ($V_5$, $V_6$, and $aV_L$) in association with an infarct confined to the apical one-third of the lateral wall, whereas there were others in which QRS abnormalities appeared in only one or two of these leads, despite the presence of infarction in the apical one-half of the lateral wall. There were five cases in which definitely abnormal QR or QS complexes were not found in either Lead $V_5$, $V_6$, or $aV_L$ (Cases 35, 36, 38, 56, 82). A detailed discussion of each of these cases will be given later.

*Correlation of the QRS-T Pattern in the Precordial Leads With the Distribution of the Infarct Between Endocardium and Epicardium.*—The infarct involved the apical one-third or more of the anteroseptal and lateral walls in fifty-six cases and the middle one-half of the anteroseptal and lateral walls in one case. The anteroseptal portion of the infarct was transmural in thirty-eight cases and was confined to the subendocardial one-fourth to three-fourths in the other nineteen. In eight of these, the subendocardial one-half to three-fourths of the anteroseptal wall was infarcted, and in eleven only the subendocardial one-fourth to one-half was involved. Although the anteroseptal portion of the infarct was transmural in thirty-eight, the extension into the lateral wall was confined to the subendocardial layer in fourteen of these, leaving twenty-four cases with transmural infarction of all or part of the apical one-third of the lateral wall. The transmural extension into the lateral wall reached or closely approached its junction with the posterior wall in fourteen cases and was limited to the anterior one-half or less of the apical aspect of the lateral wall in the other ten. The lateral portion of the infarct was confined to the subendocardial one-fourth to three-fourths of the wall in the remaining thirty-three cases and involved more than the anterior one-half of the apical aspect of the lateral wall in twenty-four of these and less than this in nine.

*QRS Pattern in Transmural Infarction.*—There was excellent correlation between the QRS pattern in Leads $V_3$ and $V_4$ and the pathologic findings in twenty-nine of the thirty-eight cases with transmural infarction of the anteroseptal wall. A smooth or notched QS complex was recorded in both Leads $V_3$ and $V_4$ in nineteen of these and in either $V_3$ or $V_4$ in the other ten. An abnormal QR pattern, characterized by a Q wave which exceeded 0.02 second in duration from onset to nadir and amounted to 25 per cent or more of the amplitude of the succeeding R, was found in these leads in Cases 80, 50, and 72. The terminal R in Case 80 could be correlated with patches of preserved muscle in the subepicardial layer. The small late R in $V_3$ and $V_4$ in Case 50 was more difficult to explain, since the apical one-half of the anterior wall was completely replaced by fibrous tissue. The upstroke may have been derived from intact muscle in the basal portion of the anterior wall. The findings in Case 72 were unusual and will be discussed in detail later along with those in the remaining six cases (Cases 34, 35, 36, 45, 56, 77), where an initial R rather than a Q was found in precordial leads over the infarct.

There was satisfactory correlation between the QRS pattern in Leads $V_5$ and $V_6$ and the pathologic findings in twelve of the twenty-four cases of transmural infarction of the lateral wall. A smooth or notched QS was found in both Leads $V_5$ and $V_6$ in three and in $V_5$ alone in nine of these cases. The rarity of a QS complex in $V_6$ can be explained by the fact that the transmural lesion rarely occupies more than the apical one-third of the lateral wall. Activation of uninfarcted portions of the lateral wall presumably gave rise to an R wave following the initial downstroke. An abnormal QR complex was recorded in both $V_5$ and $V_6$ in five cases and in $V_5$ alone in three cases. The late R wave was probably derived from portions of the lateral wall beyond the border of the lesion, but might have been accounted for in some of the cases by preserved muscle found within the infarct. Four of the patients in whom transmural infarction of the anteroseptal wall was accompanied by an initial R in Leads $V_3$ and $V_4$ also displayed an initial upstroke in $V_5$ and $V_6$ in association with transmural infarction of the lateral wall (Cases 34, 35, 36, 77).

*RS-T Pattern in Recent Transmural Infarction.*—The QS complexes associated with recent transmural infarction were usually accompanied by abnormal elevation of the RS-T junction and by straightening or upward convexity of the RS-T segment. The associated T waves were at first monophasic and upright, as exemplified by Leads $V_3$ and $V_4$ in Case 24 (Fig. 3,*C*), and subsequently underwent a progressive cove-like inversion, as described and illustrated elsewhere.[12] The QS and RS-T complexes were comparable to those registered through epicardial leads in animals with infarcts which have extended from endocardium to epicardium, but have not completely destroyed the subepicardial muscle.[14] Although the QS complex was representative of a transmural lesion, the RS-T contour indicated the presence of subepicardial muscle that was injured, but not dead. Similar RS-T and T-wave patterns are observed in animals with injury localized to the subepicardial layer and in human pericarditis, and are differentiated from the RS-T and T-wave patterns of myocardial infarction by the fact that they are associated with essentially normal QRS complexes.

The QS complexes overlying areas of recent transmural infarction in Cases 39, 40, and 41 were accompanied by only slight RS-T elevation and an upwardly concave RS-T segment and upright T wave, which exhibited no significant change in serial tracings over periods of six days, five days, and two days, respectively. The QRS-T complex in the first four precordial leads in Case 39 was an almost exact reciprocal of that in Lead $aV_F$, which reflected the potential variations of the uninfarcted diaphragmatic wall of the left ventricle. In some animals with experimental infarcts, a comparable QS deflection, elevated concave RS-T segment, and upright T wave were consistently recorded in repeated tracings through overlying epicardial leads. These findings were almost identical with those obtained through a lead from the ventricular cavity and were reciprocal to those registered through a direct lead from the epicardium of the opposite normal wall.[14] The similarity of both the QRS and RS-T complexes in epicardial leads to those in cavity leads indicated that the intervening muscle was completely dead and contributed no electromotive force, but merely served as a

conducting window for the transmission of cavity potentials to the surface. These deductions were supported by the autopsy findings, which revealed complete destruction of all muscle in the subjacent wall.

Thus, central zonal patterns associated with recent transmural infarction may be classified into two types, according to the contour of the RS-T segment: (1) QS followed by abnormal RS-T elevation and a straightened or upwardly convex RS-T segment, which undergoes characteristic changes in serial tracings; (2) QS followed by slight RS-T elevation, an upwardly concave RS-T segment, and upright T wave, which tends to remain constant in serial tracings.

*QRS Pattern in Subendocardial Infarction.*—Isolated cases have been reported[16,17] of recent infarction of the subendocardial portion of the anterolateral wall, manifested by preservation of the initial R waves and acute RS-T depression in Leads I and IVF. If a sufficient number of precordial leads are taken, an abnormal QR complex or a very coarsely notched QS deflection should be demonstrable. Patterns of this type were recorded in Leads $V_3$ and $V_4$ in eleven of the nineteen patients with infarction of the subendocardial one-fourth to three-fourths of the anteroseptal wall and corresponded closely with the pathologic findings. A QS with smooth or slightly slurred or notched ascending and descending limbs was registered in Cases 49, 57, 66, and 151, despite the fact that the infarct did not extend through the entire wall. The discrepancy between electrocardiographic and autopsy findings was not great in Cases 49 and 57, since the infarct extended through the subendocardial three-fourths and two-thirds of the walls, respectively, in these cases. An infarct limited to the subendocardial one-half of the wall in Case 151 was manifested by a splintered QS in Lead $V_4$. A smooth QS recorded in $V_3$ and $V_4$ in Case 66 could not be correlated with the fact that the infarct of the free portion of the anteroseptal wall was confined to the subendocardial one-fourth. However, the infarct in this case also involved the greater part of the left side of the septum. This gave rise to diagnostic signs in Leads $V_1$ and $V_2$ and probably was also responsible for the QS deflection in $V_3$ and $V_4$, as a result of displacement of the transitional zone to the left. Four cases of subendocardial anterior infarct (Cases 38, 44, 51, 82) remained, in which Leads $V_3$ and $V_4$ displayed an atypical finding, namely, an initial R wave. These will be discussed along with the six cases of transmural anterior infarct in which an initial upstroke was found in Leads $V_3$ and $V_4$.

There was good correlation between the QRS pattern in Leads $V_5$ and $V_6$ and the pathologic findings in twenty-seven of the thirty-three cases of infarction of the subendocardial one-fourth to three-fourths of the apical one-third or more of the lateral wall. An abnormal QR pattern was recorded in Lead $V_5$ or in $V_5$ and $V_6$ in twenty-six of these and a W-shaped QRS was registered in the other case. The remaining cases require individual discussion. The original tracing of Case 53 showed a smooth QS complex in both Leads $V_5$ and $V_6$, but a subsequent tracing showed a QR complex in these leads, which corresponded closely with the infarct of the subendocardial two-thirds of the apical portion of the lateral wall found at autopsy. The experience with this case merely illustrates the fact that a QS complex may be recorded early in the course of infarction, even though the subjacent myocardium is not entirely dead. With recovery of the

subepicardial layer, a late R wave may appear. The infarct in Case 31 was transmural in the anterior wall and became subendocardial in the lateral wall. The QS complex recorded in Lead $V_5$, as well as those in $V_3$ and $V_4$, was probably referable to the lesion of the anterior wall, and the QR complex of Lead $V_6$ conformed to the lesion of the lateral wall. A QS complex was found in Leads $V_3$, $V_4$, and $V_5$ of Case 49 in association with infarction of the subendocardial three-fourths of the anterolateral wall. A serious discrepancy between the QRS pattern in Leads $V_5$ and $V_6$ and the infarction of the subendocardial portion of the lateral wall was encountered in only three cases (Cases 38, 56, 82), where an initial R wave was recorded in both leads. These cases are discussed later.

*RS-T Pattern in Recent Subendocardial Infarction.*—Experimental injury localized to the subendocardial layer causes acute RS-T depression in overlying leads.[18] Acute coronary insufficiency characteristically produces transitory ischemia and injury of the subendocardial layer, manifested by transient RS-T depression in left ventricular leads, as exemplified by Case 38. In sixteen cases of this series, autopsy disclosed recent or organizing infarction, which appeared to be confined to the subendocardial portion of the anterolateral or lateral wall of the left apex. Precordial leads overlying the subendocardial lesion revealed abnormal RS-T depression in three cases, isoelectric RS-T junction with cove inversion of the T wave in three cases, and elevation of the RS-T junction and upward convexity of the RS-T segment in ten cases. The degree of upward displacement of the RS-T segment in these ten cases was not as great as that found in most transmural lesions, but the contour of the RS-T segment and T wave resembled that resulting from localized lesions of the subepicardial layer. Injury to this layer was therefore postulated, despite the apparent limitation of the infarct to the subendocardial one-third to two-thirds of the wall. In the three patients with isoelectric RS-T junction and cove inversion of the T wave, the infarct was in the process of organization and had apparently progressed beyond the stage of injury.[19]

*Causes of an Initial R in the Last Four Precordial Leads in the Presence of a Large Subendocardial or Transmural Anterolateral Infarct.*—The registration of an initial R in Leads $V_3$ and $V_4$ in the presence of a transmural or subendocardial infarct of the apical one-third or more of the free anteroseptal wall of the left ventricle is a very atypical finding, but was encountered in ten of the fifty-seven cases (Cases 34, 35, 36, 38, 44, 45, 51, 56, 77, 82). An initial upstroke in Leads $V_5$ and $V_6$ is likewise a very atypical finding in the presence of a transmural or subendocardial infarct of the apical one-third or more of the lateral wall, but was encountered in seven of the foregoing cases (Cases 34, 35, 36, 38, 56, 77, 82). These cases collectively exemplify the usual causes for difficulty or failure in the diagnosis of large anterolateral infarcts from the precordial electrocardiogram, and therefore will be discussed in detail. The causes for the registration of an initial R rather than a Q in Leads $V_3$ and $V_4$ in the presence of a subendocardial or transmural infarct of the anteroseptal portion of the apex and for a similar finding in $V_5$ and $V_6$ in the presence of a comparable lesion in the lateral aspect of the apex may be classified as follows:

1. *Displacement of the transitional zone to the left* may occur as a result of (a) shift of the entire heart farther into the left side of the thorax secondary to intrathoracic disease, (b) right ventricular dilatation, (c) clockwise rotation of the heart about its anteroposterior and longitudinal axes, (d) marked backward rotation of the apex about the transverse axis of the heart, and (e) various combinations of the foregoing factors. When the transitional zone is displaced to the vicinity of the anterior axillary line, the first four precordial leads will reflect principally the potential variations of the right ventricle and right side of the septum. Hence, an RS pattern like that normally found in Leads $V_1$ and $V_2$ may be recorded in $V_3$ and $V_4$ in the presence of infarction of the anteroseptal wall of the left ventricle, as illustrated by Case 44. Furthermore, under these circumstances, an anteroseptal infarct which does not extend into the lateral wall may be manifested by an abnormal QS or QR complex in Leads $V_5$ and $V_6$, but not in $V_3$ and $V_4$, as will be exemplified by Cases 67 and 68, to be reported in the next communication. Rarely, the transitional zone may be displaced into mid-axilla or beyond. Under these circumstances, signs of an extensive infarct of the anterolateral wall of the left ventricle may not be referred to any of the six customary precordial leads, as exemplified by Case 72. The first five precordial leads and $aV_L$ in this case displayed a similar Q, late R, and simultaneous intrinsicoid deflection. These findings indicated that all of these leads reflected the potential variations of the right ventricle and the right side of the septum and could be correlated directly with the dilatation of the right ventricle and infarction of the septum found at autopsy. Since Lead $V_6$ showed a transitional complex, $V_7$ and $V_8$ would have been needed in this case for exploration of the anterolateral wall of the left ventricle and for the ante-mortem detection of the extensive infarction found in this region at autopsy.

2. *Left bundle branch block* was present in Case 82 and completely obscured an old, healed infarct of the subendocardial one-half of the anterolateral wall. Activation of the septum from right to left, necessitated by the conduction defect, caused early positivity of the left ventricular cavity and thus an initial upward deflection in all precordial leads facing the left ventricle. This prevented the registration of a Q wave through precordial leads overlying the anterolateral infarct and thus accounted for the failure of the electrocardiogram to reveal diagnostic signs. When left bundle branch block occurs as a result of extensive infarction of the septum, the destroyed septum may contribute no electromotive force and may merely transmit the negative potentials developing early in the right ventricular cavity (as a result of activation of the outer wall of the right ventricle) to the left ventricular cavity, thereby permitting the registration of a Q wave in precordial leads over an anterolateral infarct.[20]

3. *Registration of the electrocardiogram soon after the onset of symptoms and before the myocardial changes have progressed to the point of obliteration of the response to the activating impulse.* Significant RS-T displacement without QRS abnormalities is a familiar finding in spontaneous or induced angina pectoris and might be expected in electrocardiograms obtained shortly after the onset of attacks that eventuate in myocardial infarction. For example, abnormal

RS-T depression, typical of acute subendocardial injury, without significant alteration in the QRS, was found in an electrocardiogram obtained two and one-half hours after the onset of an attack in Case 38 and completely disappeared the following day. Death occurred in a second attack six days later and autopsy revealed a very early ringlike infarct, involving the subendocardial one-half of the entire circumference of the left ventricle. If the age of the lesion was correctly estimated from the microscopic sections, all electrocardiograms were obtained prior to the onset of the infarct. Hence, this case should probably not be classed among those characterized by failure in the development of a diagnostic QRS pattern in Leads $V_5$, $V_6$, or $aV_L$. Nevertheless, an infarct evenly distributed throughout the subendocardial one-half of the entire circumference of the left ventricle[21] might be expected to cause abnormal reduction in the R wave without abnormal Q waves in left ventricular leads.

Significant RS-T displacement without an abnormal QR or QS complex might be expected in electrocardiograms obtained early in the course of an attack that ends in myocardial infarction, since the onset of symptoms probably antedates the development of histochemical changes responsible for the QRS abnormalities by a variable period. Marked RS-T elevation has been demonstrated within sixty to ninety seconds after coronary ligation in animals,[22] whereas the development of abnormal initial downward deflection is delayed for minutes or hours.[23]

An electrocardiogram obtained four hours after the onset of the pain in Case 77 showed extreme RS-T elevation in Leads $V_3$, $V_4$, and $V_5$ associated with a broad initial R wave of normal voltage. At death, eleven hours later, a very early transmural anterolateral infarct was found. The registration of a broad R instead of a Q in the precordial leads may have been due to an acute injury at a stage which slowed, but did not abolish, activation of the anterolateral wall. An electrocardiogram taken eight hours after the onset of the pain in Case 36 displayed typical RS-T elevation in Leads $V_4$ and $aV_L$, but merely showed an abnormally small initial R in $V_4$, $V_5$, and $V_6$ and a minute QR in $aV_L$ too low in voltage to be diagnostic of lateral infarction. At death, fifty-eight hours later, recent transmural infarction of the apical portion of the anterior and lateral walls was found. The findings in this case were best explained by the assumption that the lesion, at the time of the electrocardiogram, had reduced, but not completely obliterated, the myocardial response to the activating impulse. This hypothesis was not adequately tested in these cases, because of failure to obtain a second electrocardiogram, but was strongly supported by the findings in Case 139, to be reported in detail later. The first electrocardiogram, taken four and one-half hours after the onset of the pain in Case 139, showed marked RS-T displacement with normal R waves in Leads $V_4$, $V_5$, and $V_6$, whereas a second electrocardiogram, taken forty-four hours later, showed significant reduction in the initial R of Leads $V_4$ and $V_6$ and a QR complex in $V_5$ that conformed closely with the localized anterolateral infarct found at autopsy. The experience with these cases emphasizes the importance of obtaining further electrocardiograms when the original tracing, taken soon after the onset of symptoms, is inconclusive.

4. *Patchy infarction with preserved islands of muscle in the subendocardial layer or scattered through the wall.* An initial upstroke may be present in precordial leads over lesions of this type,[24] particularly when there is coexistent infarction of the greater portion of the posterior wall. The registration of a QS or an abnormally reduced R in precordial leads over an incompletely infarcted wall probably depends, in part, upon the magnitude of the negative potentials which build up in the left ventricular cavity during activation of the intact portion of the wall. These negative cavity potentials are available for transmission to the precordium through the dead portions of the infarcted wall and thus might be expected to oppose positive potentials referred to the precordium during activation of intact remnants of muscle within the infarct. When the infarct is confined to the anterolateral wall, the relatively great negative potentials developing in the cavity, as the result of activation of the intact posterior wall, tend to obliterate the relatively weak positive potentials developed from activation of remnants of muscle within the infarct, thereby leading to the registration of a QS complex in overlying precordial leads. When most of the posterior wall is likewise infarcted, the negative cavity potentials may be sufficiently reduced so that they fail to counteract even the weak positive potentials produced by activation of islands of preserved muscle in the infarct. This was regarded as the most likely explanation for the small initial R waves recorded in Leads $V_3$ through $V_6$ in Case 35 and for those recorded in Leads $V_3$ and $V_4$ in Cases 45 and 51.

5. *Localized complete transmural anterolateral infarction complicated by extensive infarction elsewhere in the left ventricle.* In Case 56 small initial R waves were found in leads from the precordium, covering a ventricular aneurysm consisting exclusively of fibrous tissue. Since precordial leads over the aneurysm subtended portions of intact myocardium beyond the boundaries of the aneurysm, positive potentials developing during activation of the surrounding myocardium could have been transmitted to the electrode over the aneurysm. At the onset of ventricular activation, the magnitude of these potentials at the precordial surface over the aneurysm was apparently greater than that of negative potentials transmitted through the cavity in the aneurysmal wall, as a result of the marked reduction in the latter potentials due to a coexistent infarction of the apical one-half of the septum and lateral wall and most of the posterior wall.

6. *Infarction of the left side of the septum,* in the absence of left bundle branch block, may cause local delay in passage of the impulse and thus indirectly favor activation of intact remnants of septal muscle by impulses distributed through the Purkinje plexus of the right side of the septum. Activation of the septum by impulses passing from right to left causes early positivity of the left ventricular cavity and thus an initial R in precordial leads overlying an infarct of the anterior wall of the left ventricle. This mechanism was believed responsible for the minute initial R in the precordial leads in Case 34.

*Estimation of the Age of the Infarct From the Electrocardiogram.*—The finding of a characteristic abnormality in the QRS complex is indicative of the presence of infarction, but gives no clue as to the age of the lesion. A significant increase in

the degree of QRS abnormality in one or more leads of serial tracings, as in Cases 21 and 42, may be construed as evidence of extension of the infarct, or a significant decrease may be attributed to recovery of damaged muscle consequent upon healing, provided one can be reasonably certain of a constant position of the electrode in reference to the heart.

Estimation of the age of the lesion is generally based chiefly on the RS-T and T-wave patterns. Positive conclusions are not justifiable from the examination of a single electrocardiogram without other clinical data, because of the fact that an elevated, domelike, monophasic, upright RS-T segment and T wave or cove inversion of the T wave, identical with that found during recent infarction, may persist indefinitely as a fixed residue. This is especially prone to occur when there is extensive destruction and fibrous replacement of the wall, sufficient to lead to a ventricular aneurysm,[7] as illustrated by the four patients whose tracings are reproduced in Fig. 15. The abnormal RS-T segments and T waves probably represented cavity potentials transmitted through the aneurysm without modification when the wall was completely replaced by fibrous tissue or transmitted with slight alteration when it contained muscle remnants capable of activation and repolarization. A presumptive diagnosis of recent infarction might have been made from the examination of a single electrocardiogram in any of these four cases, and demonstration of the absence of significant change in serial tracings would have been necessary to prove the presence of old, rather than recent infarction.

Serial tracings during recent transmural infarction generally show the familiar RS-T evolution, consisting essentially of marked elevation of RS-T junction and domelike, monophasic, upright RS-T complex at the beginning, followed by progressive return of RS-T junction toward the isoelectric line, accompanied by deepening covelike inversion of the T wave. These changes are observed when muscle in the subepicardial layer is acutely injured, but not dead. In serial tracings during recent transmural infarction, the QS complexes are occasionally accompanied by a constant RS-T and T-wave pattern, characterized by slight elevation of the junction, an upward concave segment, and an upright T wave. These findings may occur as a manifestation of complete destruction of the subjacent wall and are presumably due to transmission of cavity potentials through the infarcted wall without modification, not only during ventricular activation, but also during repolarization. Although such findings are usually the result of an old, healed transmural infarction, their occasional association with a recent complete transmural infarct makes consideration of the clinical data essential in the differential diagnosis.

QRS and RS-T abnormalities resembling those of recent infarction may occur in serial tracings as a result of (1) old, healed infarction complicated by an acute, but independent, pericarditis, as in Case 28; (2) old, healed infarction with superimposed effects of cardiac glycosides. The effects of digitalis on the RS-T segment and T wave depend upon the direction of the major phase of the QRS. In leads with a QS complex and upright T wave, full digitalization may result in further elevation of the RS-T junction or straightening or upward convexity of the segment and increased amplitude of the T wave, as in Lead $V_4$

of Case 42. This can be recognized as a digitalis effect by the shortening of the QT interval and by the presence of the characteristic depression of the RS-T segment and inversion of the T wave in leads with prominent R waves.

*Value of the Standard Limb Leads in the Detection of Large Anterolateral Infarcts.*—Among the fifty-seven cases of infarction involving the apical one-third or more of the anterior and lateral walls of the left ventricle, there were thirty-one in which the standard limb leads were not diagnostic nor strongly suggestive of anterolateral infarction. The findings in these leads were interpreted as indicating left ventricular hypertrophy in seven of these and nonspecific abnormalities, including right or left bundle branch block, in fifteen. In the other nine cases the standard leads were diagnostic or suggestive of an associated posterior infarct, but not of the anterolateral lesion. Thus, the standard leads are of limited value even for the recognition of large anterolateral infarcts.

## SUMMARY

The findings in the Wilson precordial leads and in the standard and Goldberger limb leads have been analyzed and correlated with the pathologic findings in fifty-seven cases of infarction of the apical one-third or more of the anterior and lateral walls of the left ventricle. The infarct was distributed transmurally through the apical one-third or more of both the anteroseptal and lateral walls in twenty-four cases; it was transmural in the anteroseptal wall and subendocardial in the lateral wall in fourteen cases; and was confined to the subendocardial one-fourth to three-fourths of both the anteroseptal and lateral walls in nineteen cases.

A QS deflection was recorded in Leads $V_3$ and/or $V_4$ in twenty-nine of the thirty-eight patients with transmural infarction of the apical one-third or more of the anteroseptal wall of the left ventricle and corresponded closely with the findings at autopsy. An abnormal QR complex was present in both leads in three other cases and was explainable by the pathologic findings. Good correlation between a QS deflection in Lead $V_5$ or in both $V_5$ and $V_6$ and transmural infarction of the apical one-third or more of the lateral wall of the left ventricle was obtained in twelve of twenty-four cases and a satisfactory explanation was found for an abnormal QR complex recorded in one or both of these leads in eight other cases.

An abnormal QR or very coarsely notched QS complex was present in Leads $V_3$ and $V_4$ in eleven of the nineteen patients with infarction of the subendocardial portion of the anteroseptal aspect of the left apex and conformed closely with the pathologic findings. A smooth or slightly notched QS deflection found in these leads in four additional cases was adequately explained. Good correlation between an abnormal QR pattern in Lead $V_5$ or in both $V_5$ and $V_6$ and infarction of the subendocardial portion of the lateral aspect of the left apex was obtained in twenty-seven of thirty-three cases and a satisfactory explanation was found for a smooth or slightly notched QS complex recorded in one or both of these leads in three other cases.

An initial upstroke was recorded in Leads $V_3$ and $V_4$ in ten cases, despite the presence of subendocardial or transmural infarction of the anteroseptal aspect of the left apex, and a similar finding was obtained in Leads $V_5$ and $V_6$ in seven of these cases, in spite of a comparable lesion in the lateral wall of the left apex. The causes for the registration of an initial R, rather than a Q, under these circumstances, were as follows: (1) displacement of the transitional zone leftward to the anterior axillary or mid-axillary line; (2) left bundle branch block; (3) infarction of the left side of the septum, necessitating activation of intact septal remnants from right to left; (4) early recording of the electrocardiogram soon after the onset of symptoms and before the myocardial changes have progressed to the point of obliterating the response to the activating impulse; (5) patchy infarction with preserved islands of muscle in the subendocardial layer or scattered through the wall; and (6) extensive infarction of the posterior wall of the left ventricle with consequent reduction in the opposing negative potentials available for transmission through the anterolateral infarct to the precordium.

The QS complexes associated with recent transmural infarction were usually accompanied by abnormal elevation of the RS-T junction and straightening or upward convexity of the segment, followed by progressive covelike inversion of the T wave in serial tracings. This RS-T pattern indicated the presence of subepicardial muscle that was injured, but not dead. In three cases, the QS complexes were accompanied by slight RS-T elevation, upwardly concave RS-T segment, and upright T waves, which exhibited no significant change in a repeat tracing a few days later. These findings were correlated with recent transmural infarction, which had completely destroyed the subjacent myocardium. Recent subendocardial infarcts were generally accompanied by upward displacement of the RS-T segment, less marked in degree, but similar in contour to that customarily found in transmural infarction and attributable to injury to the subepicardial layer. A less common, but more characteristic finding in recent subendocardial infarction consisted in acute RS-T depression, attributable to injury localized to the subendocardial layer. A positive differentiation between recent and healed infarction could not be made from a single electrocardiogram because of the tendency for abnormal RS-T elevation and/or cove inversion of the T wave to remain as a permanent finding in ventricular aneurysm.

The electrocardiograms were taken by Miss Josephine McDonald and were retouched by Miss Evelyn Erickson and Miss Geraldine Chesney.

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# AN EXPERIMENTAL STUDY OF ACUTE PULMONARY ARTERIAL OBSTRUCTION, WITH SPECIAL REFERENCE TO THE PRECORDIAL ELECTROCARDIOGRAM

JACK FLASHER, M.D.,* HIRAM E. ESSEX, PH.D.,† AND
ARLIE R. BARNES, M.D.‡
ROCHESTER, MINN.

INTEREST in pulmonary embolism dates from its first description by Virchow in 1846, although White[38] has stated that cases of dyspnea, rapid breathing, and blood spitting had been mentioned as early as 1679. The work of Cohnheim remains as the classic contribution in this field.[24,40] McGinn and White[24] and Barnes[1] were the first authors to describe electrocardiographic changes caused by this disease entity. There is general agreement as to what the standard limb lead electrocardiogram may show in cases of acute pulmonary embolism; however, the frequency of diagnostic changes is rarely stated by the various authors. Apparently this method of diagnosis is used generally only in cases of severe pulmonary embolism or in cases in which the alternative diagnosis of cardiac infarction is considered. Certainly, with the advent of the use of Dicumarol in the treatment of pulmonary embolism, it would be highly desirable to be able to ascertain the time of the occurrence of the first and often undramatic pulmonary embolism in a given case. With this in mind, we investigated multiple "unipolar" precordial leads as well as standard limb leads in dogs in which nonfatal pulmonary embolism had been produced. We were especially interested in studying the incidence of electrocardiographic changes as well as the value of the precordial leads.

McGinn and White,[24] Barnes,[1,2] Sokolow, Katz, and Muscovitz,[34] Currens,[11] Stewart and his co-workers,[35] Durant and associates,[14] Katz and Walsh,[20] and many other authors have contributed to our knowledge of the electrocardiographic changes in acute pulmonary embolism in man. The alterations may consist of: inversion of $T_3$ (may be cove plane); presence of $Q_3$ (although the true "$Q_3$ pattern" of Wilson is not present); the RS-$T_2$ take-off is usually low (with "staircase ascent"); prominent $S_1$ (there may be a right axis deviation); and reversal of $T_4$ over the right precordium. Occasionally a slight widening of the QRS complex is noted, or there may be a slightly low origin of $T_1$, or a slightly elevated RS-$T_3$. Currens[11] studied twenty-five selected cases of proved pulmonary embolism in which some electrocardiographic abnormalities were present and he listed the frequency of the various changes. These were

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*Fellow in Medicine.
†Division of Experimental Medicine, Mayo Foundation.
‡Division of Medicine, Mayo Clinic.

all patients in whom necropsy was performed not long after the pulmonary embolism. He found inversion of $T_3$ and reversal of T in $CR_2$ in twenty-one cases and the presence of $S_1$ in twenty cases; the presence of a $Q_3$, RS-$T_2$ depression, and inversion of the T wave in Lead IV R were somewhat less frequent. The only abnormality was confined to the precordial leads in seven cases and to the limb leads in two cases. (The interpretation of the former is somewhat questionable since previously he stated that inversion of $T_3$ was present in twenty-one cases.) The foregoing series of thirty cases included only five cases in which recent cardiac infarction as well as acute pulmonary embolism was present. However, coronary occlusion was present in only one of the five cases; presumably, in the other four cases, the concomitant shock was responsible for the coronary insufficiency that produced the cardiac infarction. Some recent experimental work confirming this impression will be mentioned later.[25] Sokolow and his associates[34] noted that evolutions of T, RS-T, or Q did not occur except for an occasional delay in the appearance of Q, or an increase in depression in RS-$T_1$ or RS-$T_2$. They found the complete electrocardiographic pattern of McGinn and White[24] in only five of fifty cases of acute pulmonary embolism (necropsy was performed in twenty of the fifty cases). In nine of the cases there were no electrocardiographic changes, but in the remaining cases the electrocardiograms disclosed significant changes, nonspecific abnormalities, disturbances of origin and conduction of impulses, or some of the changes found in cases of myocardial infarction.

Especial interest in the precordial leads has been shown by Wood,[41] Myers and Stofer,[31] Wilson and associates,[39] Barnes,[2] and Katz.[18] According to the last-mentioned author, the precordial electrocardiogram may show a depression of the RS-T segment in Lead $CF_5$ (with a "staircase ascent") and, characteristically, an inverted T wave in $CF_2$. He mentioned that in a large percentage of cases of pulmonary embolism, nonspecific changes without diagnostic significance may occur and that all electrocardiographic stigmata disappear within three weeks at the very most, and usually within one day to one week. An exception to this is encountered in an occasional case in which multiple pulmonary emboli occur. Apparently, such emboli produce chronic strain of the right ventricle. Under these circumstances, the electrocardiographic pattern of chronic strain of the right ventricle may persist indefinitely. One of us (A. R. B.) has observed two such cases. Belt[4] reported four cases in which right ventricular hypertrophy was associated with recurrent pulmonary embolism or thromboembolism (post-mortem study); no electrocardiographic studies were mentioned. Myers and Stofer used Wilson's precordial leads of the so-called unipolar type in forty cases of acute strain of the right ventricle (not due to pulmonary embolism in all cases). They found sharply inverted T waves with convex RS-T segments in Leads $V_1$, $V_2$, and $V_3$*; this was most marked in $V_1$ and least in $V_3$; therefore, it differed from that found in anteroseptal cardiac infarction. Sokolow and his associates reported slight elevation of RS-T in Lead $CF_2$ in some of their cases.

*These are unipolar leads introduced by Wilson.

The electrocardiogram made after pneumonectomy in man has been studied by Semisch and Merves[33] and by Barnes.[3] The last-mentioned author did not find significant changes in the electrocardiogram although he followed his patients serially for as long as two weeks in certain instances. He also added that in only three of eleven consecutive cases of definite clinical acute pulmonary embolism did he find typical changes. Semisch and Merves, on the other hand, noted "helpful" electrocardiographic changes in thirteen of fourteen cases in which lobectomy or pneumonectomy had been performed, although in only two cases were the changes "definite." Within twenty-four hours, the electrocardiogram in ten of the cases had reverted to normal. These cases in which pneumonectomy was performed are mentioned only to indicate the amount of pulmonary obstruction necessary to produce electrocardiographic changes in man; it is apparently less than the amount necessary in the dog.[12,15,26,29]

The electrocardiographic changes in the dog caused by acute pulmonary embolism have received attention from many investigators. The nature of these changes is in some dispute. Winans, Goode, and Ashworth,[40] who used ten dogs in which they produced graduated constriction of the pulmonary arteries, noted that most often the earliest and most constant change was a depression of the RS-$T_2$ take-off (or a downward swing of RS-$T_2$ ending in an inverted T); RS-$T_3$ depression and $T_2$ and $T_3$ inversion were noted slightly later and less frequently. Further constriction produced irregular terminal changes. Robb and Robb,[32] who used graded constriction of the pulmonary arteries, first noted RS-T depression in Leads II and III. With the last-mentioned changes they noted widening of the base of the right ventricle roentgenographically. Mendlowitz,[30] however, noted elevation of RS-$T_2$ and RS-$T_3$ and inversion of $T_2$ and $T_3$ in the animals in which he had produced large pulmonary embolism. In one of his animals he did find RS-$T_2$ and RS-$T_3$ depression. Most of the animals died or appeared to be near death as a result of the embolism. Love and his co-workers[23] observed some further variations. Much of this variability is thought to be due to the extreme lateral mobility of the dog's heart. Placing and keeping the animal in exactly the same position from day to day does not offer too great an obstacle if the lateral position is used; however, the heart is then in an unnatural position, being thrown to the left or right side of the thorax. The variability of the standard lead electrocardiogram has been well brought out in the work of Betlach.[5] He especially noted the almost complete unpredictability of the T waves. Katz, Soskin, and Frisch[19] and Lalich, Cohen, and Walker[21] also made original contributions that supported the finding of great variability of the electrocardiogram of the dog.

By using needle electrodes and following Lead II serially, Cabitt, Altschule, and Zamcheck[9] observed reversal of the T wave in all of eleven dogs that had undergone unilateral pneumonectomy (whether control was positive or negative). They also observed transient cardiac arrhythmia in five of the animals. Most other investigators claim that much greater pulmonary arterial occlusion must be obtained to produce electrocardiographic changes; in most cases, enough occlusion to produce right ventricular dilatation must be present. Special interest in the dynamics of experimental acute obstruction of the pul-

monary artery has been shown by many investigators.[15,28,29,37] Malinow, Katz, and Kondo[25] recently studied the so-called pulmonocoronary vagal reflexes in the dog and concluded that changes attributed to these reflexes are in reality a result of functional coronary insufficiency resulting from the low systemic blood pressure that is associated with the more severe types of acute pulmonary embolism. Villaret and his associates,[37] by means of studies on rabbits, noted that section of the vagus nerves increased by sevenfold the quantity of emboli necessary to produce death; section of the cervical sympathetic nerves reduced the quantity necessary by fourfold. Giving atropine and ephedrine delayed the occurrence of sudden death. De Takats, Beck, and Fenn[36] also considered vagal reflexes important in producing the low systemic blood pressure.

## METHOD OF STUDY

Acute pulmonary embolism was produced twenty-four times in ten dogs by rapid serial intravenous injections of a variable number of small particles; these particles were glass beads 3.0 mm. in diameter, rape seeds 1.5 to 2.0 mm. in diameter, or particles of sand 1.0 to 2.0 mm. in diameter. The glass beads were the most satisfactory. These particles were lined up in glass tubes of various lengths and physiologic solution of sodium chloride was used to wash them into the external jugular or femoral vein. Serial injections were continued until moderate tachypnea was produced; an increase of ten to fifty respirations per minute that persisted for at least two to three minutes was considered a good end point and was achieved in most cases. This increase in respiratory rate has been found to be a reliable indication of sublethal but large pulmonary emboli in dogs. Work along this line has been reported by several investigators.[6,7,26,29,30,36] With rare exceptions, this method produced embolism of a notable but nonfatal degree, although there was a wide variation in the number of particles necessary; for instance, from 150 to 350 rape seeds. The dogs weighed 9 to 15 kilograms and were apparently healthy mongrels. Both injections and electrocardiograms were made while the dogs were under anesthesia produced by the intravenous injection of 25 to 30 mg. of pentobarbital sodium per kilogram of body weight.

Electrocardiograms were made two or three times before the initial injection of embolic material, as well as between experiments and fifteen to 130 minutes after the completion of each experiment. The animal was placed on his back for the injections of the embolic material and on his right side for the electrocardiograms. A Sanborn Cardiette, with the sensitivity reduced one-half, was used throughout the experiment. The limb lead plates were applied with electrode jelly after the area was clipped and washed just as is done in man. Copper rivets, with heads about 1.0 cm. in diameter, were used as precordial electrodes; the skin was first prepared as for the limb leads. Five to nine precordial electrodes were used and they were held in place by means of perforations in a stiff rubber belt. They were spaced 1.25 inches (3.18 cm.) each way from the midline and were numbered I-IIII, IIII, IIII-I, IIII-II, II-III, IIII-III, IIII-IIII, IIII-IIIII and IIII-IIIIII) going from the right

side to the left side across the sternum; the sternum lead was II-III. The belt was applied so that Lead IIII-IIII was on the fifth rib. To check on the accuracy of the position of the belt, occasional control electrocardiograms were made with Lead IIII-IIII at the fourth, sixth, and seventh ribs, as well as at the fifth rib. Burnett[8] in a recent paper discussed changes in the precordial electrocardiograms due to the position of the exploring electrode. In our experiments, the limb lead electrocardiograms were the standard type, but the precordial electrocardiograms were the Goldberger[16] modification of the unipolar Wilson type.

## RESULTS

In the limb leads there were significant changes in only five of the twenty-four electrocardiograms made after the injection of embolic material; the most marked changes were produced in a dog in which a fatal embolism was produced unintentionally. These changes consisted of elevation of RS-$T_2$ in four experiments and elevation of RS-$T_3$ in two; a negative $T_2$ and $T_3$ and a diphasic $T_2$ and $T_3$ (where the controls had quite consistently shown a positive T) appeared in one episode. In the animal in which fatal embolism was produced, there was a marked depression of RS-$T_2$; RS-$T_3$ and RS-$T_1$ were also somewhat depressed, and a previously negative $T_1$ became positive (Fig. 1). One

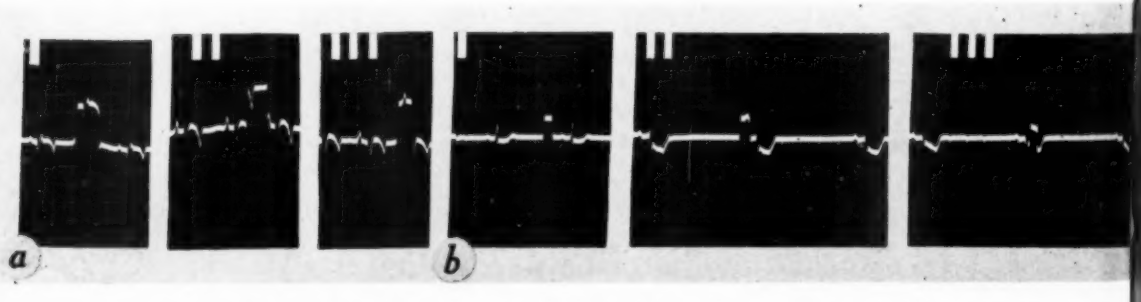


Fig. 1.—Pulmonary embolism: *a*, before embolism; *b*, after embolism. In *b*, the RS-$T_2$ depression is marked; a lesser degree of RS-T depression is present in Leads I and III. $T_1$ has become positive. The control electrocardiogram, *a*, shows the extreme inversion of the T waves in all leads that may be encountered in apparently normal dogs. (In *a*, 1.0 cm. = 1.0 mv., and in *b*, 0.5 cm. = 1.0 mv.; in all subsequent figures, the sensitivity is reduced so that 0.5 cm. = 1.0 mv., as can be seen in the occasional standardizations.)

animal exhibited a slight shift of the electric axis to the right. The precordial leads in these experiments showed very minor changes. Decreased positivity of the T wave in leads over the right precordium appeared in the electrocardiogram of one animal and slight elevation of RS-T in leads over the left precordium appeared in two other animals. These changes were of doubtful significance.

These changes are certainly quite minimal; perhaps, as previously mentioned, this is due to the fact that a greater degree of pulmonary obstruction is necessary to cause dynamic changes in the dog than is apparently necessary in man. Whether pulmonary arterial spasm is an important factor in either the

dog or man is still a matter of conjecture. However, after reviewing the literature, we believe that these findings in dogs would not be in marked disagreement with the electrocardiographic changes found in instances of minor pulmonary embolism in man. One gets the impression that electrocardiographic changes are f equent in pulmonary embolism in man probably because (1) only cases in which these changes are present are usually reported and (2) usually only patients with the more severe clinical manifestations are investigated electrocardiographically. As noted previously, the precordial electrocardiogram was of little additional aid. However, this does not necessarily obtain in instances of more severe pulmonary embolism in the dog or in man. The frequent spontaneous reversal of the T waves in any of the standard leads makes it very difficult to evaluate the significance of the not infrequent reversal of the T wave in many of our dogs after the production of embolism. However, even the precordial lead T waves, although quite predictable in the dog, did not show any reversals. Currens and Barnes[12] quoted two different groups (de Takats, Beck, and Fenn[36] and Leriche, Fontaine, and Friedmann[22]) who found only minor obstruction of the pulmonary artery present in 20 and 30 per cent of patients dying of pulmonary embolism. This apparently does not obtain in the dog. Cullen and Rovenstine[10] reported three instances of sudden death of human beings when the hilus of the lung was ligated or cut with the electric cautery. Whether pulmonary arterial spasm occurs in man is conjectural; in the dog, it apparently is not a factor, for Gibbon and his associates[15] have demonstrated that at least 85 per cent of the pulmonary arterial flow must be blocked before death results. A better laboratory animal for the study of pulmonary embolism would be one in which smaller emboli could occasionally cause death and in which the normal electrocardiogram was of a more constant nature. Possibly the cat would fulfill the latter qualification[13]; in the dog, the use of direct ventricular leads might serve this same purpose.[39]

Even with larger and often fatal pulmonary emboli, the electrocardiographic changes in the dog are quite variable, judging from the findings of some of the authors mentioned.[9,30,32,40] To test this, we produced graded acute pulmonary arterial obstruction in seven dogs by using an adjustable snare around the pulmonary artery, somewhat as first used by Winans, Goode, and Ashworth.[40] We studied these animals with serial limb lead electrocardiograms until shortly before death. It was interesting to note that a marked degree of constriction was necessary to produce any changes in the electrocardiogram. Mann, Herrick, Essex, and Baldes[27] have demonstrated that constriction of the lumen of small arteries in animals may be surprisingly great without changing the rate of flow through the vessel as measured by the thermostromuhr. We did obtain significant electrocardiographic changes in all of these animals, but rather than being readily predictable, as indicated in the work of any one of a number of authors, the results were much like a composite of their work (Figs. 2 and 3). In general, RS-T deviation did occur, especially in Leads II and III, but this might be either elevation or depression, or indeed both might exist; elevation may be noted first or sometimes depression may be noted first. The T waves were not helpful, nor were there any $S_1$ or $Q_3$ waves where they were

not already present to the same degree in the control electrocardiogram. Since $Q_3$ is one of the changes observed in pulmonary embolism in man, it is of interest to note that Goldberger[17] expressed the opinion that unipolar limb leads are often necessary in the interpretation of standard limb lead Q waves, espe-

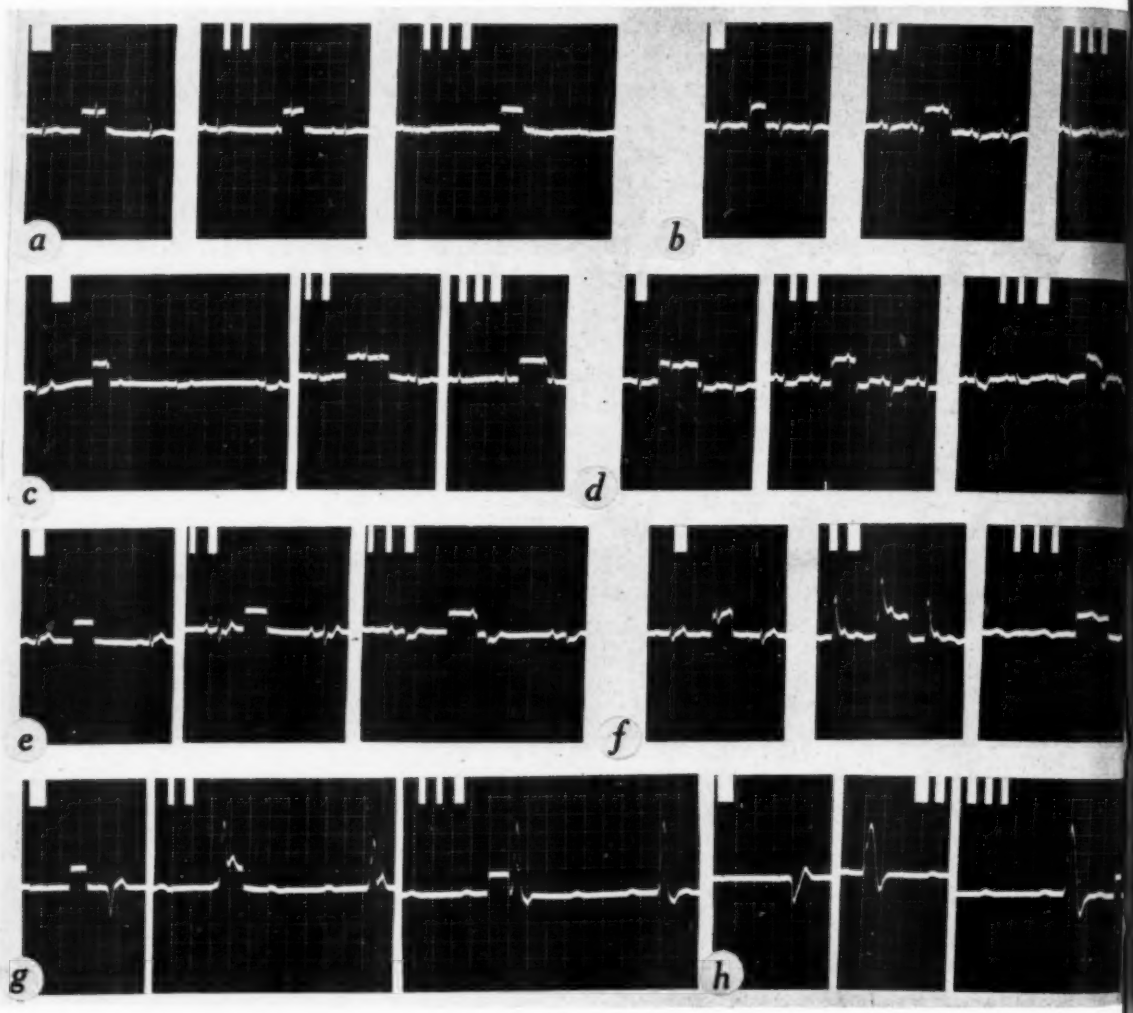


Fig. 2.—Pulmonary arterial constriction: *a*, before constriction; *b* through *h*, after gradually increased constrictions. The changes in order of appearance are: deepening of $S_1$; depression of $RS\text{-}T_1$; depression of $RS\text{-}T_2$ and $RS\text{-}T_3$, and a terminal disturbance of rhythm.

cially $Q_3$ waves. He noted that occasionally a large Q or QS in Lead III merely reflects a large R wave in the $V_2$ lead. Terminally, auriculoventricular dissociation, ventricular extrasystoles, auricular fibrillation, and other nonspecific changes in rhythm and conduction were often present in the electrocardiograms of our dogs. We also produced fatal pulmonary embolism in two dogs with an

overdosage of seeds; both animals showed definite and similar changes in the precordial electrocardiogram as well as in the limb leads. The changes in the limb leads were similar to those in the other instances of fatal pulmonary embolism just mentioned. The precordial electrocardiograms were made serially and showed depression of the RS-T segment in leads over the left precordium

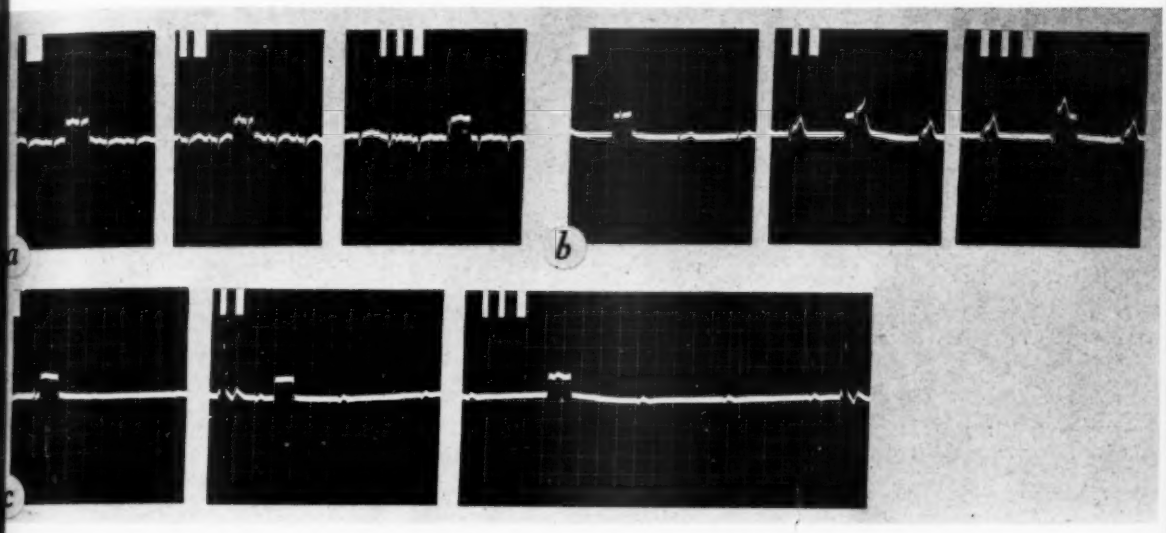


Fig. 3.—Pulmonary arterial constriction: *a*, before constriction; *b* and *c*, after gradually increased constriction. The changes consist of *b*, a well-marked elevation of RS-$T_2$ and RS-$T_3$, and *c*, a terminal disturbance of rhythm.

and elevation of the RS-T segment in leads taken over the right precordium. Inversion of the T wave in leads recorded over the right precordium, which is characteristic of the electrocardiogram of man, was not present (Fig. 4).

## SUMMARY

It must be concluded that in the dog the electrocardiogram, including multiple unipolar precordial leads, is of limited value in the diagnosis of minor pulmonary embolism. In major pulmonary embolism in the dog, there are usually definite electrocardiographic changes, both in the limb leads and in the unipolar precordial leads. In the limb leads, the most constant change is deviation of the RS-T segment in Leads II and III; this may be either upward or downward. In man, the upward deviation of RS-$T_2$ has not been reported. In the precordial leads, there was depression of the RS-T segment in the left precordial leads and elevation of the RS-T segment in the right precordial leads. In man, elevation of the RS-T segment in the right precordial leads has rarely been reported.[34]

We did not attempt to evaluate the origin of these electrocardiographic changes; it has been suggested variously that they are due either to right ventricular strain or to myocardial anoxia.

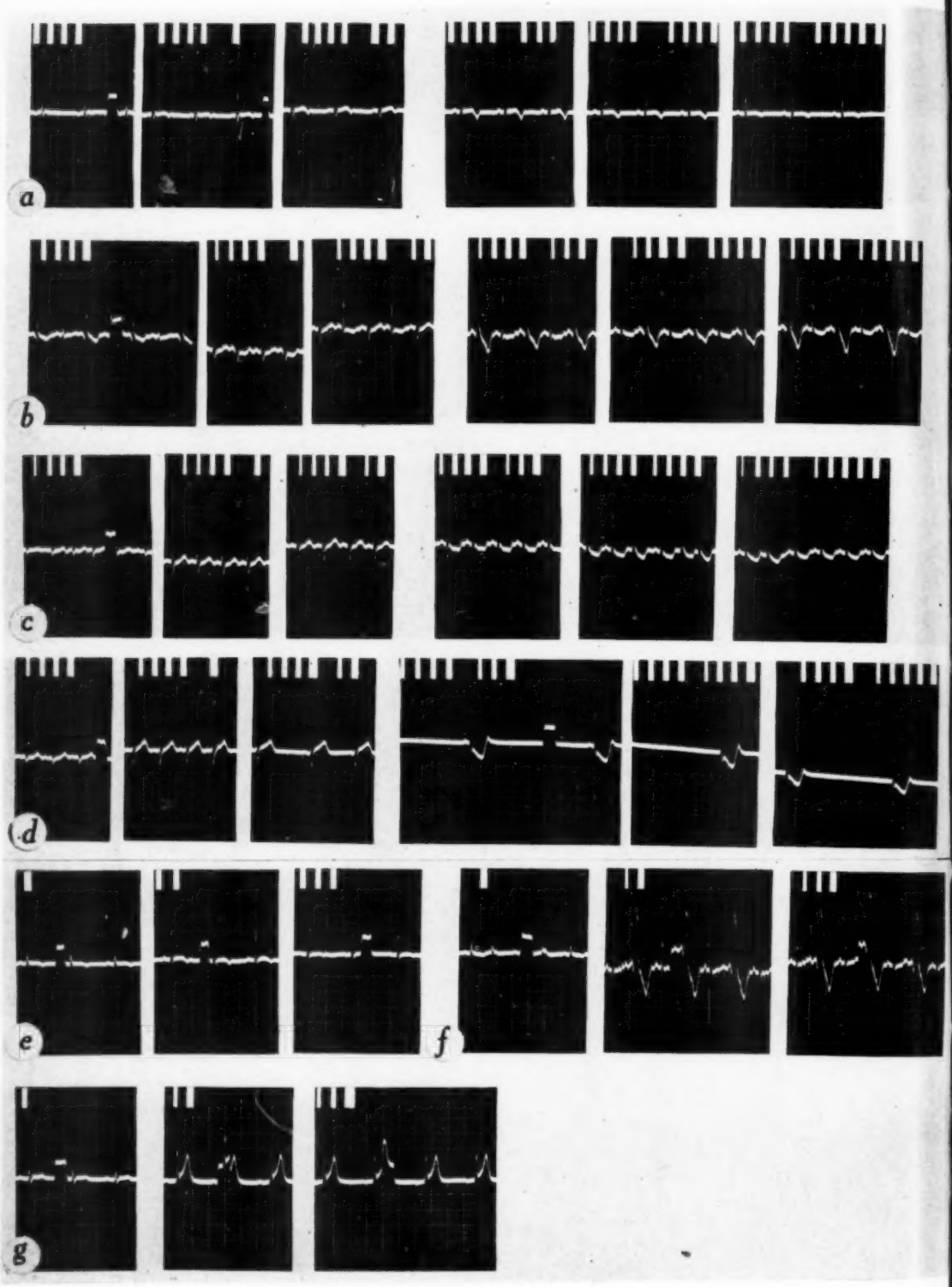


Fig. 4.—Pulmonary embolism: *a* through *d*, "unipolar" precordial leads; *a*, before embolism; *b*, *c*, and *d*, after gradually increased number of emboli; *e* through *g*, standard limb leads; *e*, before embolism; *f* and *g*, after gradually increased number of emboli.

In the precordial leads, aside from the disturbances of rhythm, the significant changes are RS-T depression in leads made over the left precordium (IIII-III through IIII-IIIII) and S-T elevation over the right precordium IIII through IIII-II). The limb leads show the development of an S wave in Lead I, elevated R-T junction in Leads II and III, and high amplitude of $T_2$ and $T_3$.

Previously in this paper attention has been called to the limitations of the electrocardiogram in the diagnosis of pulmonary embolism in man. But if a series of electrocardiograms are obtained in the first few days after pulmonary embolism occurs and if these are critically analyzed, valuable diagnostic aid can frequently be obtained. This study of the electrocardiograms of dogs in which pulmonary embolism has been induced experimentally would appear to support pessimism regarding the value of the electrocardiogram in the clinical diagnosis of pulmonary embolism. But it is by no means certain that these experiments in dogs duplicate the exact degree or exact mechanisms involved in pulmonary embolism in man. Furthermore, the electrocardiogram of the dog is more variable than is the electrocardiogram of man, so that electrocardiographic changes in the dog have to be of greater magnitude to have diagnostic significance.

While the results of these experiments should serve to warn us that the electrocardiogram often fails to aid in the diagnosis of minor pulmonary emboli in man, it should not be concluded from this study that the procedure possesses very limited clinical value.

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# THE OXYGEN CONTENT OF CORONARY VENOUS BLOOD AS AFFECTED BY ANOXIA AND CYTOCHROME C*

JAMES E. ECKENHOFF, M.D., AND JOSEPH H. HAFKENSCHIEL, M.D.
PHILADELPHIA, PA.

CYTOCHROME C has recently been advocated by Proger and Dekaneas[1,2] for the treatment of angina pectoris and coronary occlusion. The basis for its use is that under conditions of anoxia, it will enable the heart to remove some of the 75 to 80 per cent unused oxygen found in mixed venous blood in the right ventricle. Thus, the arteriovenous oxygen difference would widen (for example, from 4 volumes per cent to 6 volumes per cent), indicating increased uptake of oxygen from the blood by the anoxic tissues.[3] In patients demonstrating S-T segment depression in the electrocardiographic tracings during inhalation of 10 per cent oxygen mixtures, the injection of cytochrome C has been followed by the disappearance of the depression within two minutes.[1] This has been attributed to relief of myocardial anoxia through the action of cytochrome.

The theory upon which cytochrome is used presupposes several things, namely: (1) Under conditions of anoxia there are significant amounts of oxygen in coronary venous blood that could be utilized. (2) If such oxygen were present, cytochrome C could actually effect its removal.

Since a method was available for obtaining direct evidence on these questions,[4] it was deemed desirable to investigate the following factors pertaining to the oxygen content of coronary venous blood: (1) What are the normal values? (2) What is the effect of anoxia, per se, on these values? (3) What is the effect of the intravenous injection of cytochrome C?

## METHODS

Two different methods have been utilized in this study:

1. *The Bubble Flowmeter Method.*—The techniques used here were the same as were outlined in a previous report.[4] In brief, dogs, averaging 17 kilograms in weight, were anesthetized with pentobarbital sodium intravenously. The animals' heparinized blood was then circuited from a cannulated right carotid artery, through the bubble flowmeter into a cannulated anterior descend-

From the Department of Pharmacology and The Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, and The Department of Anesthesiology, Hospital of the University of Pennsylvania.

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ing coronary artery. Coronary venous blood was obtained from a cannulated great cardiac vein and arterial blood from the femoral artery. The pneumothorax was evacuated and the animals allowed to breathe spontaneously.

2. *Catheterization Technique.*—In these experiments, the coronary sinus of the intact, lightly anesthetized dog was catheterized with fluoroscopic guidance, the method used being that reported by Goodale and associates[5] and utilized for the measurement of coronary blood flow[6] by the nitrous oxide method of Kety and Schmidt.[7,8] Coronary venous blood was thus obtained near the junction of the great cardiac vein and the coronary sinus. Arterial blood samples were collected from a femoral artery.

Blood samples were withdrawn into oiled syringes, the tips of which were filled with heparin. The arterial and venous samples were collected synchronously. The syringes were capped, immediately immersed in ice water, and placed in a refrigerator until the blood was analyzed for oxygen and carbon dioxide content by the method of Van Slyke and Neill.

The cytochrome C used in these experiments was obtained in sterile ampules,* each ampule containing 50 mg. of cytochrome C dissolved in 10 c.c. of normal saline. All injections were made intravenously in amounts varying from 3.8 to 12.5 mg. per kilogram of body weight.

## RESULTS

The first consideration was the oxygen content of coronary venous blood obtained under our "normal" experimental conditions (that is, with the animal breathing room air or a gas mixture containing more than 21 per cent oxygen). Table I summarizes the data obtained in two groups of experiments in which: (a) the control animals were breathing 100 per cent oxygen (bubble flowmeter experiments) and (b) the control animals were breathing room air (catheterization experiments). The arterial and venous values are averages for the number of experiments indicated. In both groups the oxygen content of coronary venous blood was "normally" low. The coronary arteriovenous difference was about 13 volumes per cent, as compared with an average right ventricular arteriovenous difference of 4 volumes per cent.

TABLE I. "NORMAL" OXYGEN CONTENT OF CORONARY VENOUS BLOOD

| | NO. EXPTS. | NO. OBSERV. | ARTERIAL $O_2$ (VOL. %) | VENOUS $O_2$ (VOL. %) | A-V $O_2$ DIFF. (VOL. %) |
|---|---|---|---|---|---|
| 100% oxygen | 10 | 19 | 19.0 | 5.7 | 13.3 |
| Room air | 10 | 17 | 16.4 | 2.9 | 13.5 |

*Kindly supplied by the Wyeth Institute of Applied Biochemistry, Philadelphia, Pa.

Table II summarizes our findings on the effect of anoxia on the coronary venous oxygen content. The control averages, with the animals breathing either room air (catheterization experiments) or 100 per cent oxygen (bubble flowmeter experiments), as well as the observations on the same animals with 10 per cent and 8 per cent oxygen, are presented for each group. These data indicate that with the low oxygen mixtures inhaled, the amount of oxygen remaining in the coronary venous blood was very small.

TABLE II. EFFECT OF ANOXIA ON CORONARY VENOUS OXYGEN CONTENT

| | NO. EXPTS. | ARTERIAL $O_2$ (VOL. %) | VENOUS $O_2$ (VOL. %) | A-V $O_2$ DIFF. (VOL. %) |
|---|---|---|---|---|
| Room air (control) | 4 | 17.5 | 5.4 | 12.1 |
| 10% oxygen | | 12.8 | 3.2 | 9.6 |
| 100% oxygen (control) | 5 | 19.8 | 6.5 | 13.3 |
| 8% oxygen | | 9.5 | 2.0 | 7.5 |

Table III contains the average findings from a group of five experiments during which animals, made anoxic by the inhalation of 10 to 14 per cent oxygen mixtures, were given cytochrome C intravenously. The bubble flowmeter technique was used in all of these experiments. The control blood samples were withdrawn immediately before the injection of the cytochrome and the second pair collected an average of nine minutes after the injection.

TABLE III. EFFECT OF CYTOCHROME C ON THE CORONARY A-V OXYGEN DIFFERENCE

| | CONTROL | AFTER CYTOCHROME C (AV. OF 9 MIN.) |
|---|---|---|
| Artery $O_2$ (vol. %) | 13.7 | 12.2 |
| Vein $O_2$ (vol. %) | 4.2 | 3.5 |
| A-V difference (vol. %) | 9.5 | 8.7 |

No. experiments, 5.
Amount of cytochrome C injected, 3.8 to 7.8 mg/kg.

Table IV presents the oxygen data from three additional experiments where the catheterization technique was employed. The table indicates the chronological order in which the blood samples were removed and the oxygen and cytochrome C were administered.

TABLE IV. EFFECT OF CYTOCHROME C ON THE OXYGEN CONTENT OF CORONARY VENOUS BLOOD

| EXP. | CONTROL | LOW $O_2$ MIXTURE INHALED (% $O_2$) | 10 MIN. | 15 MIN. | 20 MIN. | 30 MIN. | CYTOCHROME (MG./KG.) | 15 MIN. | 30 MIN. | 45 MIN. |
|---|---|---|---|---|---|---|---|---|---|---|
| 3. Artery (vol. %) | 20.7 | 14 | | 18.5 | | 18.7 | 6.2 | 17.4 | | 19.6 |
| Vein (vol. %) | 3.3 | | | 2.8 | | 3.0 | | 2.8 | | 3.0 |
| 4. Artery (vol. %) | 17.8 | 10 | 12.7 | | 12.4 | | 4.2 | 11.9 | 11.2 | |
| Vein (vol. %) | 8.6 | | 2.0 | | 1.8 | | | 1.8 | 1.9 | |
| 5. Artery (vol. %) | 18.7 | 10 | 12.2 | | 12.5 | | 12.5 | 11.9 | 12.0 | |
| Vein (vol. %) | 7.3 | | 2.7 | | 2.7 | | | 2.3 | 2.0 | |

In only one of the eight animals did the arteriovenous oxygen difference increase (Table IV, Experiment 3). This occurred because the arterial oxygen content increased, apparently because of a change in the character of respirations which became full and deep following the injection of the cytochrome C. No such response was noted in the other dogs.

## DISCUSSION

Data on the extremely low oxygen content of coronary venous blood have been presented before by Harrison, Friedman, and Resnik[9] and by Shipley and Gregg.[10] Our own work[4] has confirmed this and served to re-emphasize an important fact not sufficiently appreciated by many clinicians. Recent publications concerning the fortuitous catheterization of the coronary sinus of man[11,12] have led to the procurement of coronary venous blood samples whose oxygen content agrees well with that of samples obtained in the animal studies just referred to. It becomes difficult to see how appreciably larger quantities of oxygen can be removed by the heart when, under normal conditions, it is removing 75 to 80 per cent of the oxygen delivered to it.

Under conditions of anoxia, the oxygen supply to the myocardium is maintained primarily by an increase in the volume of coronary blood flow.[4] The shift in oxygen content of coronary venous blood is seldom more than 2 to 4 volumes per cent; consequently, a demand for more oxygen must be met by an increased coronary flow. This train of events is illustrated by the data contained in Table V. These observations were made in an experiment on the effect of anoxia on the coronary circulation and cardiac metabolism.[4] It is evident that under the conditions of anoxia, there are no significant quantities of oxygen left in the coronary venous blood that could be removed even if cytochrome C were to perform its expected action.

TABLE V. EFFECT OF ANOXIA ON THE CORONARY CIRCULATION
(Experiment 0-10*; Weight of Dog, 16.3 Kilograms)

| $O_2$ MIXTURE INHALED (% OXYGEN) | 100 | 21 | 16 | 12 | 8 |
|---|---|---|---|---|---|
| Cor. Blood Flow (cc/100 Gm./min.) | 54 | 82 | 106 | 176 | 264 |
| Art. $O_2$ Content (vol. %) | 19.5 | 15.7 | 11.2 | 7.9 | 4.0 |
| Cor. Vein $O_2$ Content (vol. %) | 3.5 | 2.4 | 1.8 | 1.1 | 0.6 |
| Cardiac $O_2$ Consump. (cc/100 Gm./min.) | 8.5 | 9.0 | 9.9 | 12.0 | 9.0 |

Coronary flow measured by the bubble flowmeter method.
*Pentobarbital sodium anesthesia.

As indicated by the data contained in Tables III and IV, we could detect no effect of cytochrome C on the removal of oxygen from coronary blood. The dosage of the drug used was equal to or greater than the amounts recommended by Proger and associates.[3] While it is true that the blood samples following cytochrome (Table III) were withdrawn after a comparatively short interval, one would have expected the changes to have occurred, if they were going to, on the basis of the reported improvement in two minutes following the injection of the drug in patients.

Since cytochrome C did not effect the removal of oxygen from coronary blood, the possibility remained that there might have been a stimulation to the coronary flow to increase the amount of oxygen delivered to the heart (coronary flow multiplied by the arterial oxygen content).[13] Coronary blood flow was measured in four of the experiments, summarized in Table III, and in none of the four did oxygen delivery or oxygen consumption increase.

In these experiments, therefore, we were unable to demonstrate that cytochrome C could increase the removal of oxygen from coronary blood. Nor were we able to find any evidence for an improvement in the oxygenation of the myocardium such as indicated by the report of Proger and Dekaneas.[3] These negative findings are in general agreement with other recently published reports[14,15] on the effect of cytochrome C.

## SUMMARY

1. By means of the bubble flowmeter and the coronary sinus catheterization methods of investigating the coronary circulation of the dog, the "normal" values for the coronary venous oxygen content have been found to be 3 to 6 volumes per cent.

2. When 8 to 10 per cent oxygen mixtures were breathed, the oxygen content of coronary venous blood was reduced to 2 volumes per cent or less.

3. Increases in oxygen uptake by the heart were accomplished primarily by increases in the volume of coronary blood flow.

4. Cytochrome C, when injected intravenously in amounts varying from 3.8 to 12.5 mg. per kilogram of body weight, did not increase the coronary arteriovenous oxygen difference or the oxygen uptake of the heart.

We wish to express our appreciation to Dr. Carl F. Schmidt and Dr. Francis Wood for their interest and suggestions during this investigation.

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# A PORTABLE ELECTRICAL MANOMETER SUITABLE FOR CONTINUOUS INDICATION OF PERIPHERAL VENOUS PRESSURES

ALBERT A. POLLACK, M.D.,* AND EARL H. WOOD, M.D., PH.D.†
ROCHESTER, MINN.

BECAUSE of the awkwardness and difficulty in handling a water manometer in hospital wards, there is need for a simpler means of measuring venous pressure. An instrument devised to fill this need is described herein.

## MATERIAL AND METHODS

A resistance wire, strain gauge manometer coupled directly to a suitable galvanometer‡ as described by Lambert and Wood[1] for measuring and recording intra-arterial blood pressure was used.

The galvanometer, light source, and accessory optical and electrical systems were incorporated in a cabinet (Fig. 1), the outside dimensions of which are 17 by 9 by 10½ inches (43.2 by 22.9 by 26.7 cm.). The optical system consists of a light source,§ a condensing lens of 3.0 cm. focal length, the galvanometer mirror, two front surfaced mirrors measuring 1 by 4½ inches (2.5 by 11.4 cm.), mounted at opposite ends of the cabinet, and a ground glass screen incorporating a millimeter scale, 15 cm. in length. The optical distance from the galvanometer mirror to the screen is 1.06 meters. A hair line is projected onto the galvanometer mirror and brought to a focus on the ground glass screen by means of the condensing lens.¶

The electrical system exterior to the manometer consists of a stable voltage source,** the galvanometer, a small voltmeter,*** and two variable resistors. The circuit diagram is shown in Fig. 2. The batteries supply the voltage across the Wheatstone bridge circuit which is incorporated within the strain gauge manometer. One of the variable resistors serves to regulate the voltage across this Wheatstone bridge; hence, the sensitivity of the manometer. The voltage

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*Fellow in Medicine, Mayo Foundation.

†Section on Physiology, Mayo Clinic and Foundation.

§Heiland Type A galvanometer. Manufactured by the Heiland Research Corporation, Denver, Colo.

115 volt, 15 watt bulb, code 15T 8/c. Manufactured by the General Electric Company, Cleveland, Ohio.

¶In more recent models of the instrument the image of the filament of a single filament bulb (10 volt, 3.5 amp., Code T 14, manufactured by the General Electric Company, Cleveland, Ohio) has been focused onto the ground glass screen in place of the hair line. This light source is powered from a transformer (10 volt, 3.5 amp., No. AX 1162, manufactured especially for this instrument by the Audio Development Company, Minneapolis, Minn.) activated by 115 volts A.C.

**Two six-volt, four-cell Eveready lantern batteries.

***Zero to 1 milliammeter with an internal resistance of 50 ohms.

across the bridge is indicated on the voltmeter which is mounted on the front panel of the cabinet. The second resistor is used as an accessory calibrating device to check the response of the instrument to a given change in resistance in the bridge circuit. The wash bottle* for the manometer system is also contained within the cabinet. Pressure in the wash bottle can be regulated to any desired level by means of a hand bulb and a Tycos manometer which are mounted on the front panel of the cabinet (Fig. 1).

The strain gauges are attached to the top of the cabinet by means of brackets. A strain gauge manometer† with a pressure range of ±20 mm. of mercury has been found suitable for the measurement of peripheral venous pressure. When used with 10 volts across the bridge circuit, this manometer produces a galvanometer deflection of 7 mm. per centimeter of water and is linear throughout its pressure range. The sensitivity of the manometer can be reduced to any degree by reduction of the input voltage. The manometer is equipped with a lucite adapter, as described by Lambert and Wood, so that the detection and removal of air bubbles from the system is greatly facilitated. The manometer is connected to a 19 or 20 gauge hypodermic needle by means of an adapter and an 86 cm. length of 1.6 mm. I.D. polythene tubing. The volume displacement of the entire system per 10 mm. of mercury pressure is 22 cubic millimeters. The manometer system is overdamped. The instrument requires 0.75 second to register 95 per cent of the full response to an instantaneous pressure change.

The instrument weighs 21 pounds (9.5 kilograms) and is sufficiently rugged so that it can be transported by carrying. A handle is mounted on the top of the cabinet to facilitate handling of the instrument.

Venous pressure determinations with this instrument have been carried out as follows:

The patient is kept at rest in the supine position for at least fifteen minutes. If he is not lying on a rigid-topped couch, a board which is at least as long as the width of the bed and about 8 inches (20.3 cm.) wide is placed under the scapulae. The arm is abducted to form an angle of about 40° and is placed below the midthoracic level. The strain gauge is placed at approximately the same height as the antecubital space and a reading is taken with the needle lying on the skin of the antecubital space just above the vein. A 19 or 20 gauge needle is inserted into the antecubital vein and the strain gauge adapter attached when it is certain that all air bubbles have been expressed from the system. If the venous pressure is elevated to a degree that produces an off-scale deflection of the instrument, the voltage is reduced so as to bring the hair line onto the scale. The voltage is checked during the test to see that it is maintained at a constant value. The manometer system is flushed with heparinized saline solution (10 mg. sodium heparin is added to each 500 c.c. of 0.9 per cent saline solution) for a second or two before readings are made. When three similar consecutive readings, taken at intervals of approximately thirty seconds, are obtained, they are taken as the venous pressure. The venous pressure usually stabilizes to this degree in from

*A brass adapter top was devised so that an ordinary 500 c.c. Baxter bottle of sterile 0.9 per cent saline solution could be utilized.

†Model No. P5-0.4D-350, Statham Laboratories, Los Angeles, Calif.

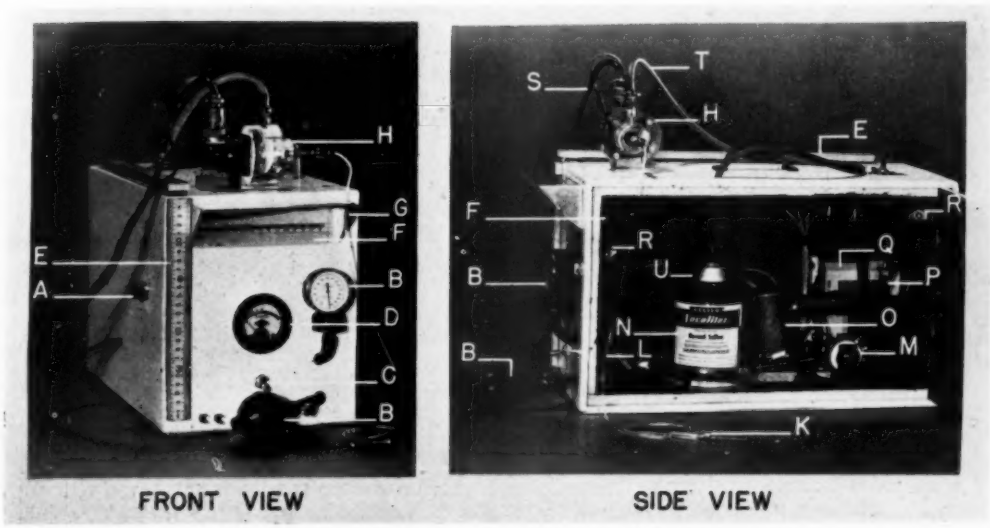


Fig. 1.—Portable strain gauge manometer. *A*, Calibration switch; *B*, pressure bulb and Tycos manometer for wash bottle; *C*, battery switch; *D*, voltmeter; *E*, calibration scale in centimeters; *F*, ground glass screen; *G*, shade; *H*, strain gauge manometer; *K*, glass adapter and needle; *L*, polythene tubing; *M*, voltage control; *N*, wash bottle; *O*, light source; *P*, galvanometer; *Q*, batteries; *R*, mirrors; *S*, lead wires; *T*, wash tubing; *U*, adapter top for wash bottle.

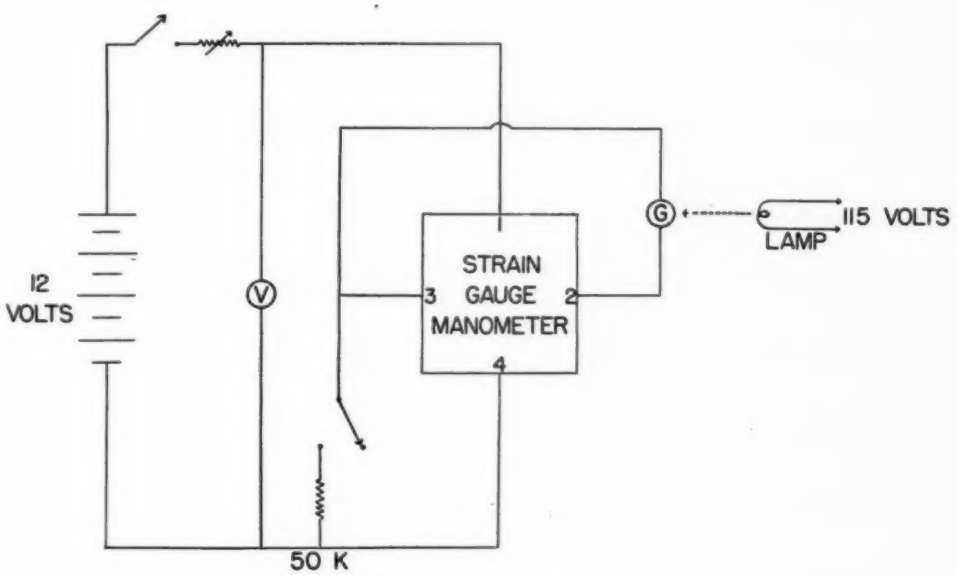


Fig. 2.—Circuit diagram. Portable strain gauge manometer.

five to fifteen minutes after the venipuncture has been completed. When stable readings are obtained, the needle is removed from the vein. The needle and a small amount of fluid are removed from the glass adapter so that the resulting meniscus lies near the middle of the barrel of the adapter. The adapter is then placed horizontally on the top of the board which was inserted under the patient's back and a reading is taken. The adapter is placed at the third intercostal space just to the right of the sternum and a second reading is taken. These two readings serve to measure the anteroposterior diameter of the patient's thorax at the level of the third intercostal space and provide a basis for determining the zero point to be selected for the venous pressure readings.

Calibration is simple and speedy. The meniscus in the adapter is leveled with different points on a vertical centimeter scale mounted on the front panel of the cabinet (Fig. 1). Readings are taken at four or five equidistant points on this scale selected so that the range of pressures encountered in the test is covered by these calibration readings. The galvanometer readings are plotted against the scale readings (centimeters of water). This calibration curve has uniformly been found to be linear. The galvanometer readings obtained during the test are readily converted to pressure (centimeters of water) by use of this calibration curve. The zero or reference point can be taken at (1) the midpoint of the anteroposterior diameter of the thorax at the level of the third intercostal space or (2) 10 cm. above the skin of the back or at any other point, covered by the calibration, which may be selected.

The venous pressure readings obtained by means of the strain gauge manometer were compared with those obtained by the use of the water manometer in the following manner: A water manometer was fixed to a wooden couch in such a fashion that the manometer was perpendicular to the couch top, with the zero of the scale at couch top level. The patient reclined on the couch top for about fifteen minutes. When the patient was in the supine position the anteroposterior diameter of his thorax was measured at the level of the third intercostal space by the use of calipers, as well as by the placing of the adapter of the strain gauge at the third right intercostal space just next to the sternum and on the couch top both before and after the test. An ordinary 20 gauge needle was inserted into the antecubital vein and attached to a three-way stopcock. The adapters of the water manometer and strain gauge manometer were then attached to the stopcock and the pressures recorded alternately after stabilization of the venous pressure.

The capillarity of the water manometer was determined as 5.0 mm. of saline solution; consequently, this figure was subtracted from the water manometer readings. Capillarity likewise becomes a factor during the calibration of the strain gauge manometer. The capillary action of the glass adapter used in these experiments supported a fluid column of 12 mm. of saline solution. This figure was subtracted from the calibration curve for the instrument. In the study of ten normal subjects between the ages of 20 and 35 years, the differences between the venous pressures as measured by the water manometer and the strain gauge manometer ranged from $-0.5$ cm. to $+0.9$ cm. of saline solution (Table I). On the average, the strain gauge readings were 0.08 cm. of saline solution above the

TABLE I. COMPARISON OF THE VENOUS PRESSURE IN NORMAL SUBJECTS AS DETERMINED BY A WATER MANOMETER AND A STRAIN GAUGE MANOMETER

| SUBJECT | VENOUS PRESSURE MEASURED BY WATER MANOMETER (CM. OF SALINE SOLUTION) | VENOUS PRESSURE MEASURED BY STRAIN GAUGE MANOMETER (CM. OF SALINE SOLUTION) | DIFFERENCE (CM. OF SALINE SOLUTION) |
|---|---|---|---|
| 1 | 11.8 | 11.9 | 0.1 |
| 2 | 9.9 | 10.2 | 0.3 |
| 3 | 9.5 | 9.9 | 0.4 |
| 4 | 10.6 | 11.5 | 0.9 |
| 5 | 12.6 | 12.7 | 0.1 |
| 6 | 13.6 | 13.2 | −0.4 |
| 7 | 13.2 | 13.1 | −0.1 |
| 8 | 10.2 | 9.9 | −0.3 |
| 9 | 9.8 | 10.1 | 0.3 |
| 10 | 10.6 | 10.1 | −0.5 |
| Average values | 11.2 ± 0.5* | 11.3 ± 0.4* | 0.08 |

*The figure following the ± sign is the standard error of the mean.

readings obtained by the water manometer. This difference, however, was not considered statistically significant since the $p$ value was greater than 0.5 (Table I).

## COMMENT

The literature contains many reference points for the site of the right auricle with reference to various parts of the body in the supine position. Bloomfield and his associates,[2] after taking measurements from lateral roentgenograms, felt that 5.0 cm. below the angle of Louis was the point from which to calculate venous pressure as well as right heart pressure. Winsor and Burch[3] have described a phlebostatic axis and a phlebostatic level for measurement of venous pressures. Lyons, Kennedy, and Burwell[4] reviewed the literature and listed several tables with different reference points and the normal values for the venous pressure as determined from these points by the various authors. They found that the great majority of the range of normal venous pressures falls between 5.0 cm. and 15 cm. of saline solution. They measured the height of the right auricle from the skin of the back in frozen sections of cadavers as well as by means of fluoroscopy and felt that 10 cm. from the skin of the back was an accurate point from which to measure venous pressure in an adult. However, difficulty has been encountered in use of such a reference point for female patients since the anteroposterior diameter of the thorax in some cases is approximately 10 cm. or less.

At this laboratory it was decided to use the midpoint of the anteroposterior diameter of the thorax measured at the level of the third right intercostal space since this is about the level of the middle of the right auricle as given by Cunningham.[5] In ten normal subjects the range of venous pressure was found to fall within 5.0 to 15 cm. of saline solution measured both by water manometer and

strain gauge with the midpoint of the anteroposterior diameter of the thorax at the level of the third intercostal space as the reference point.

When the deflection of the galvanometer was read, it was noted that rhythmic fluctuations of the hair line ranged from 2.0 to 5.0 millimeters. These fluctuations are caused partly by respiration and partly by transmission of the venous pulse wave. The mean value of these pressure fluctuations has been taken as the venous pressure.

This instrument* is simple to operate and a technician was easily taught to determine venous pressures without assistance in a few days. Since the instrument weighs 21 pounds, it can be carried for short distances and rolled on a cart if greater distances must be covered by the technician. The instrument we use is transported to two different hospitals, as well as to the cardiovascular laboratory, in its daily use. The accuracy of this type of manometer already has been discussed by Lambert and Wood, and the comparison of measurements made by the water manometer and strain gauge demonstrates further the degree of exactness of the determinations.

## SUMMARY

A portable electrical manometer suitable for continuous indication of peripheral venous pressure has been described. Resting venous pressure in the arm in the supine position was determined in ten normal subjects and found to be 11.3 cm. of saline, with a range of 9.9 to 13.2 centimeters.

## ADDENDUM

By use of a strain gauge the range of which is ±200 mm. of mercury (Model P 6-4D-250), this instrument has been used for continuous measurement of pressure during atrial catheterization. Because the instrument can be read in the dark, pressures can be determined as the catheter is being advanced under the fluoroscope, thus greatly facilitating the procedure of determining the exact moment of entry or withdrawal from the right ventricle or pulmonary artery.

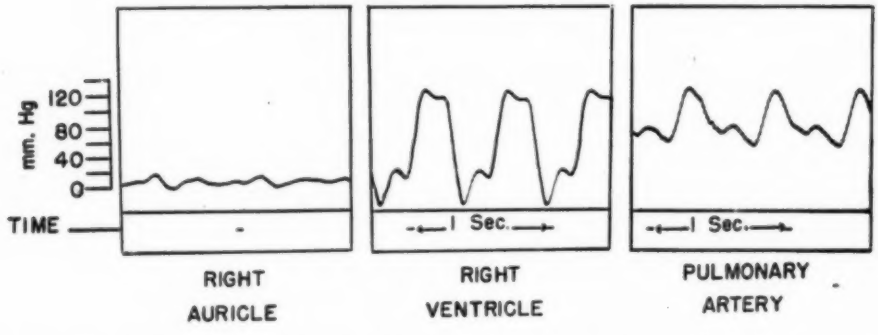


Fig. 3.—Photokymographic tracings of pressures during atrial catheterization. The patient was an 11-year-old white boy with patent ductus arteriosus complicated by pulmonary hypertension.

*A modification of this instrument can be obtained from the Waters Conley Company, Rochester, Minn.

Photographic recording of the pressures has been made simultaneously with the visual readings (Fig. 3) by connecting a recording galvanometer* in series with the galvanometer of the instrument. The frequency characteristics of the combined manometer-catheter system precludes the use of the instrument in its present form for accurate studies of ventricular pressure pulse contours.

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*A Heiland Type A galvanometer incorporated in a Heiland Type A 401 R-6 oscillograph. Manufactured by the Heiland Research Corporation, Denver, Colo.

# CAN THE LONGITUDINAL ANATOMICAL AXIS OF THE VENTRICLES BE ESTIMATED FROM THE ELECTROCARDIOGRAM?

ALBERT HYMAN, M.D.,* NEW ORLEANS, LA., R. B. FAILEY, M.D., CINCINNATI, OHIO, AND RICHARD ASHMAN, PH.D., NEW ORLEANS, LA.

IN AN earlier paper[1] it was stated that it is possible to estimate with reasonable accuracy the longitudinal anatomical axis of the human ventricles ($\hat{H}$) from the QRS complex of the electrocardiogram. By use of an adaptation of the method first proposed by Gardberg and Ashman,[2] estimates of the axis, $\hat{H}$, were made for thirty-six cases in Master's book.[3] In thirty-four of thirty-six cases, the axis measured on the x-ray plate and the axis estimated from the electrocardiogram differed by not over 7 degrees. In one case the difference was 8°, and in another it was 12 degrees. It was admitted that the estimate may unconsciously have been influenced by knowledge of the teleroentgenogram. Further evidence was adduced to demonstrate that estimates from the electrocardiogram are fairly accurate, but the evidence was indirect. Since we proposed making use of the method in a study of the electrocardiographic changes in thyrotoxicosis, a direct test of the question seemed to be desirable.

## METHOD

The direction of H was determined by orthodiagram in a series of fifty normal persons, most of whom were on the staff of or employed by the Cincinnati General Hospital. The standard limb-lead electrocardiogram was also taken on each of these individuals, the body position being the same as that during the fluoroscopic examination. Children were excluded from the series. The electrocardiograms were then sent to the third author, with no additional information. The latter excluded two of these fifty electrocardiograms because of the presence of a delay in right bundle branch conduction. (This is seen in a small percentage of persons who present no clinical evidence of heart disease.) Two other records were excluded because the technique was untrustworthy. A fifth electrocardiogram was rejected because it was clearly abnormal, the P-R intervals being long and variable and the QRS complexes low and of unusual configuration. Thus, the electrocardiograms of forty-five subjects remained. In each of these subjects, $\hat{H}$, the longitudinal ventricular axis, was estimated according to the method previously described.[4,5] In most instances, the estimate was based on the charts shown in those papers. In only a few cases was the QRS loop of the vector-

From the Cardiac Laboratory of the Cincinnati General Hospital, Cincinnati, and the Department of Physiology, Louisiana State University, School of Medicine, New Orleans.

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*At present on the Resident Staff of the Charity Hospital of Louisiana at New Orleans.

cardiogram constructed as an aid in finding the $\hat{H}$ direction. In addition, in each case the mean manifest QRS axis ($\hat{A}_{QRS}$) and its magnitude ($A_{QRS}$), and also $\hat{G}$ (the mean manifest QRS-T axis or ventricular gradient of Wilson) and its magnitude (G), were estimated.[6]

## RESULTS

Table I shows the results of our study. In the first column is the subject's number. In the second column is the direction of $\hat{H}$ as measured by the orthodiagram. In six instances, two separate estimates are shown for the same subject. In these the $\hat{H}$ axis was re-estimated; the second estimate is given below the first. In the third column the electrocardiographic estimate of $\hat{H}$ is given; and in the fourth column is shown the difference in degrees between the estimates by the two methods. It will be observed that in thirty-seven of the forty-five subjects the angle between the two estimates of $\hat{H}$ is less than 10°; in forty-three cases it is less than 12°; in one case it was 14°; and in one case it was 15 degrees.

When the estimates of $\hat{H}$ based on the electrocardiogram reached Cincinnati, the six subjects in whom the difference between the two estimates exceeded 10° were re-examined. As the table shows, in four of these six subjects, remeasurement lessened the discrepancy between the findings by the two methods. In two subjects the second orthodiagram confirmed the first. (Remeasurements are shown in parentheses in the table.)

## DISCUSSION

The first question which must be asked is: Are the apparent agreements between the $\hat{H}$ axes, estimated by the two methods, significant? Is it not possible that if one were to guess $\hat{H}$ in all instances to be +40° (which is about the average direction), the agreement between this $\hat{H}$ and the estimate by orthodiagram would be as good as the agreement shown by the table?

An answer to this question can be obtained only by statistical methods. The first step is to assume that the $\hat{H}$ axis given by the orthodiagram is the correct one. Then, for each electrocardiographic estimate of $\hat{H}$ there is either no error (the two estimates being in agreement), or else the electrical estimate is in error because the indicated direction of $\hat{H}$ is to the right or to the left of the orthodiagrammatic finding. We can plot these "errors" and calculate their standard deviation from the mean. On the average, the $\hat{H}$ axis is electrically estimated to point 1.94 ± 0.57° to the right of its "true" (orthodiagram) direction. The standard deviation of the discrepancies between the two estimates is 5.66 ± 0.41 degrees.* This figure suggests that in a comparable series of persons it should be possible to estimate $\hat{H}$ from the electrocardiogram alone with an error of less than 15° in ninety-nine out of one hundred cases. It should be noted that these calculations are based on the original orthodiagrammatic

*If the standard deviation is calculated, using the $\hat{H}$ found on re-examination, it falls to 4.95 ± 0.35 degrees.

measurements. No correlation was found between the body build and extent of error.

But it may be true that if we guessed all axes to be +40°, as we have suggested, the errors would be no greater. When this is done, the standard devia-

TABLE I. COMPARISON OF THE ELECTROCARDIOGRAPHIC AND ORTHODIAGRAMMATIC ESTIMATES OF $\hat{H}$

| SUBJECTS' NUMBER | $\hat{H}$ FROM ORTHODIAGRAM (DEGREES) | $\hat{H}$ FROM ECG (DEGREES) | DIFFERENCE, ECG ESTIMATE TO RIGHT OR LEFT OF ORTHODIAGRAMMATIC (DEGREES) |
|---|---|---|---|
| 3 | 47 | 48 | 1 R |
| 4 | 50 | 54 | 4 R |
| 5 | 47 | 52 | 3 R |
| 6 | 43 | 54 | 11 R |
| | (43) | | |
| 7 | 29 | 25 | 4 L |
| 8 | 48 | 42 | 6 L |
| 9 | 52 | 50 | 2 L |
| 10 | 37 | 39 | 2 R |
| 12 | 52 | 52 | 0 |
| 14 | 33 | 41 | 8 R |
| 15 | 43 | 40 | 3 L |
| 16 | 32 | 35 | 3 R |
| 17 | 44 | 54 | 10 R |
| 18 | 45 | 60 | 15 R |
| | (51) | | (9 R) |
| 19 | 49 | 60 | 11 R |
| | (49) | | |
| 20 | 47 | 50 | 3 R |
| 21 | 34 | 45 | 11 R |
| | (36) | | (9 R) |
| 22 | 51 | 42 | 9 L |
| 23 | 50 | 45 | 5 R |
| 24 | 52 | 45 | 7 L |
| 25 | 58 | 47 | 11 L |
| | (45) | | (2 R) |
| 26 | 48 | 53 | 5 R |
| 27 | 42 | 44 | 2 R |
| 28 | 35 | 35 | 0 |
| 29 | 37 | 38 | 1 R |
| 30 | 47 | 48 | 1 R |
| 31 | 45 | 41 | 4 L |
| 32 | 48 | 55 | 7 R |
| 33 | 35 | 42 | 7 R |
| 34 | 39 | 53 | 14 R |
| | (46) | | (7 R) |
| 35 | 48 | 43 | 5 L |
| 36 | 30 | 26 | 4 L |
| 37 | 35 | 40 | 5 R |
| 38 | 28 | 24 | 4 L |
| 39 | 50 | 55 | 5 R |
| 40 | 44 | 40 | 4 L |
| 41 | 43 | 42 | 1 L |
| 42 | 35 | 34 | 1 L |
| 43 | 51 | 50 | 1 L |
| 44 | 39 | 44 | 5 R |
| 45 | 38 | 42 | 4 R |
| 46 | 34 | 37 | 3 R |
| 48 | 24 | 31 | 7 R |
| 49 | 39 | 49 | 10 R |
| 50 | 27 | 29 | 2 R |

tion of the "errors" rises to 8.10 ± 0.58 degrees. The difference between this figure and 5.66 ± 0.41° is 2.44 ± 0.70 degrees. Since the difference is three and one-half times its probable error, we may conclude that the electrocardiographic estimate is considerably more reliable than an estimate of all axes as +40°.

A fairer test of the relative accuracy of the method, however, seems to be to compare the electrocardiographic estimate of $\hat{H}$ of each subject with the orthodiagrammatic estimate of the next subject on the list. When this is done, the standard deviation of the errors rises to 12.30 ± 0.88 degrees. The difference between this figure and the standard deviation of 5.66 ± 0.41 is 6.64 ± 0.97 degrees. Since that difference is nearly seven times its probable error, it is highly significant and demonstrates that $\hat{H}$ can be estimated with fair accuracy from the electrocardiogram.

Thus far in the discussion it has been assumed that the estimate of $\hat{H}$ from the orthodiagram is correct. It is our opinion that the orthodiagrammatic estimate may be as much in error as the electrocardiographic estimate. Thus, if the electrocardiogram errs in one direction and the fluoroscope in the other, the discrepancy may be large, and misleading. Some evidence tends to support this belief: (1) Careful remeasurement of $\hat{H}$ in the six subjects showing the greatest discrepancy reduced the "error" in four cases, though the remeasurements are not included in the statistical analysis. (2) In the series from Master's book, the $\hat{H}$ axis shown by the teleroentgenogram had been measured and remeasured until it was felt that the estimates were as accurate as possible. In only one of the thirty-six subjects did the "error" exceed 8°, and in that particular case it is likely that the electrocardiogram and roentgenogram were not taken with the patient in the same position. (3) Further evidence is obtained from a study of $\hat{G}$. Ashman has reported that the standard deviation of the deviations of $\hat{G}$ from their estimated average directions in a series of 164 adults was 7.38 ± 0.28 degrees. In our present series of cases, the standard deviation of $\hat{G}$, when the electrocardiographic estimate of $\hat{H}$ is used, is 7.66 ± 0.55 degrees. This latter is not significantly different from the previously reported figure. When the study of the gradient deviation is based upon the orthodiagrammatic measurements in the present series of cases, the standard deviation rises to 8.61 ± 0.62 degrees. Although the two figures are not significantly different in a statistical sense, they add some slight support to the view that the electrocardiographic estimate of H may have been more accurate than the fluoroscopic estimate in this study.

It may be noted in conclusion that the method used in estimating $\hat{H}$ from the electrocardiogram may be open to further refinement. It is, therefore, possible that greater accuracy may ultimately be attained.

## SUMMARY

The direction of the longitudinal anatomical axis of the ventricles was estimated from the orthodiagram in each of forty-five normal persons. Quite independently, the same estimate was made from the QRS complex of the electrocardiogram, taken in the same recumbent body position. The two series of

estimates were then compared. It is concluded that the form of the QRS complex correctly indicates the direction of the anatomical axis in a large majority of normal persons.

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# EVALUATION OF THE PRECORDIAL LEADS OF THE ELECTROCARDIOGRAM IN OBESITY

HARRY L. JAFFE, M.D., ELIOTT CORDAY, M.D., AND ARTHUR M. MASTER, M.D.
NEW YORK, N. Y.

IT IS well known that in obesity and other conditions associated with a transverse position of the heart the standard leads in the electrocardiogram frequently present a characteristic pattern, namely, left axis deviation and inversion of the T and P waves in Lead III[1,2]; frequently there is a large Q wave in Lead III and occasionally the T wave is low in Lead II. These changes may be difficult to differentiate from those produced by myocardial disease, particularly previous coronary occlusion with posterior infarction. For a number of years we[2] have also occasionally observed T-wave inversion in Lead $CF_4$ in normal obese persons, a finding usually considered abnormal.[3-6] Since no systematic study of the precordial electrocardiogram in obesity had been reported, an investigation was undertaken to determine whether the chest leads in obese subjects differed from those in normal persons.

The study was considered to be pertinent to two current and related controversial subjects; namely, the limits of the normal T wave in the six official chest positions[7] and the relative value of the location of the indifferent electrode, whether the right arm, left arm, left leg, or the common terminal of Wilson[8] (CR, CL, CF, or V leads). In the past, CF leads have usually been used routinely and the majority of reports in the literature, based on the use of these leads alone, state that the T wave is normally upright in Positions 2 to 6 except that it is diphasic in Lead $CF_2$ in approximately 1 per cent of cases.[3-6] Yet T-wave inversion has occasionally been observed in Lead $CF_4$ in presumably normal persons[9] and in those with autonomic imbalance or neurocirculatory asthenia.[2,10] Similar inconsistencies were encountered in CL and CR leads. Comparison of the CF, CL, and CR leads demonstrated differences between them and certain advantages were pointed out for each.[3,11,12] This resulted in considerable complexity and uncertainty in the use of chest leads. In 1934, Wilson and his coworkers[8] introduced a common terminal (unipolar, V leads), thus obviating the distorting influence of the extremity potentials on the chest leads. It is well established that the CR, CL, and CF leads, which are supposed to register the electrical activity immediately beneath the precordial electrode, are affected by the potentials from the right arm, left arm, and left foot, respectively. In other words, the "indifferent" extremity electrodes are not completely neutral. A positive extremity potential has a "negative" influence on the precordial electro-

From the Cardiographic Department, Mount Sinai Hospital, New York, N. Y.
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TABLE I. ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY-FOUR OBESE WOMEN

| PATIENT | AGE | HT. | WT. | AXIS | STANDARD LEADS | T WAVE IN CHEST LEADS |
|---|---|---|---|---|---|---|
| 1 (L. S.) | 44 | 5′6″ | 208 | LAD | $Q_3$, $T_3$ inverted | $CF_1$ inverted |
| 2 (M. H.) | 41 | 5′5″ | 396 | LAD | $Q_3$, $T_3$ inverted | $CF_1$ isoelectric |
| 3 (M. M.) | 36 | 5′6″ | 187 | LAD | $T_3$ inverted | $CF_{1,2}$ inverted |
| 4 (H. W.) | 52 | 5′2″ | 195 | LAD | $Q_3$, $T_3$ inverted | |
| 5 (S. J.) | 43 | 5′7″ | 230 | LAD | | Q present in $CF_{1,2}$; $CF_{1,4}$ inverted, varies with respiration; CR normal |
| 6 (R. K.) | 42 | 5′2″ | 172 | LAD | | $CF_1$ inverted |
| 7 (M. F.) | 39 | 5′6″ | 187 | LAD | | $CF_1$ inverted |
| 8 (A. K.) | 40 | 5′6″ | 215 | LAD | $Q_3$, $P_3$, $T_3$ inverted | $CF_1$ inverted |
| 9 (H. J.) | 37 | 5′8″ | 216 | LAD | | $CF_1$ inverted |
| 10 (B. W.) | 51 | 5′2″ | 229 | LAD | | $CF_{1,2}$ inverted; $CF_3$ inverted, varies with respiration; CR normal |
| 11 (R. A.) | 47 | 5′1″ | 186 | None | | $CF_1$ inverted |
| 12 (R. M.) | 36 | 4′7″ | 158 | LAD | | $CF_1$ inverted |
| 13 (S. A.) | 42 | 5′2″ | 260 | None | $T_1$ low | $CF_{1-6}$ inverted $CR_{4-6}$ diphasic |
| 14 (J. L.) | 21 | 5′3″ | 221 | None | | $CF_1$ inverted |
| 15 (C. M.) | 52 | 5′7″ | 244 | LAD | $Q_3$, $P_3$, $T_3$ | $CF_1$ inverted |
| 16 (M. B.) | 64 | 5′4″ | 191 | LAD | | $CF_1$ inverted |
| 17 (E. S.) | 50 | 5′1″ | 187 | None | | $CF_{1-5}$ inverted, $CF_6$ isoelectric; CR normal; after weight reduction, CF normal |
| 18 (F. H.) | 42 | 5′2″ | 160 | LAD | | $CF_{1,2}$ inverted; CR normal |
| 19 (E. K.) | 50 | 5′7″ | 206 | LAD | | |
| 20 (R. K.) | 28 | 5′6″ | 182 | LAD | | $CF_1$ inverted |
| 21 (B. Z.) | 53 | 5′8″ | 175 | LAD | | $CF_1$ inverted |
| 22 (D. S.) | 46 | 5′1″ | 156 | LAD | $Q_3$, $T_3$ inverted | $CF_{1,2}$ inverted |
| 23 (N. R.) | 50 | 5′6″ | 215 | LAD | | $CF_1$ inverted; $CF_6$ varies with respiration |
| 24 (G. S.) | 40 | 5′2″ | 194 | LAD | | Q, $CF_{1,2}$ vary with respiration; $CF_{1-3}$ inverted; CR normal |
| 25 (L. K.) | 48 | 5′6″ | 179 | LAD | normal | |
| 26 (E. C.) | 41 | 5′4″ | 192 | LAD | $Q_3$, $P_3$, $T_3$ inverted | $V_{1-6}$ low, $CF_1$ inverted |
| 27 (K. W.) | 18 | 5′6″ | 184 | None | $T_3$ inverted | $CF_1$ inverted |
| 28 (F. G.) | 38 | 5′3″ | 196 | LAD | $Q_3$, $P_3$, $T_3$ inverted | $V_{1-6}$ low, $CF_1$ inverted, $CF_2$ diphasic, $CF_{3,4}$ low; $CL_{1,2}$ inverted, $CL_3$ diphasic, $CL_{4-6}$ low |
| 29 (R. M.) | 40 | 5′4″ | 184 | LAD | $P_3$, $T_3$ inverted | $CF_1$ inverted |
| 30 (L. A.) | 48 | 5′4″ | 160 | LAD | | $CF_{1-6}$ low or inverted |
| 31 (B. A.) | 56 | 5′2″ | 162 | LAD | $Q_3$ | |
| 32 (R. G.) | 46 | 5′3″ | 166 | None | | $CF_1$ inverted, $V_1$ low |
| 33 (L. C.) | 41 | 5′2″ | 220 | LAD | $Q_3$, $P_3$, $T_3$ inverted | $V_{1-6}$, $CF_{1-6}$ low; $CL_{1-4}$ inverted or diphasic; $CL_{5,6}$ isoelectric |
| 34 (M. K.) | 25 | 5′2″ | 250 | LAD | $Q_3$, $T_3$ inverted | $CF_1$ inverted, $V_{2-6}$, $CF_{2-6}$ low; $CL_{1,2}$ inverted, $CL_3$ isoelectric, $CL_{4-6}$ low |

cardiogram and a negative extremity potential has a "positive" influence. Thus, in normal persons a positive T wave in the unipolar left arm lead ($aV_L$) exerts a negative influence or subtracts from the positive voltage of the T wave in CL leads. Conversely, the normally negative T wave in the unipolar right arm lead ($aV_R$) has a positive effect on the T wave of the chest leads and increases the size of the T wave in the CR leads. As Hecht[13] pointed out, in normal persons the T wave in the precordial leads in Positions 2 through 6 as a rule is of sufficient amplitude so that the extremity influences do not produce inversion of this wave. The common terminal of Wilson is presumably nearly neutral, nullifying the extremity influences; when it is used as the indifferent electrode the exploring electrode should reflect the electrical changes taking place directly beneath it. Since there is considerable discussion concerning the validity and usefulness of unipolar leads,[14] in the present investigation they were compared with the CF, CR, and CL leads in order to determine whether the extremity potentials significantly distort the precordial electrocardiogram in obesity.

## MATERIAL

Thirty-four of forty-seven markedly obese women attending the nutrition clinic were studied consecutively. The remaining thirteen were excluded after preliminary examination revealed hypertension or evidence of cardiac disease. In the thirty-four patients retained there were no symptoms or signs of cardiac disease or hypertension; in addition, fluoroscopy, x-ray examination of the chest in the posteroanterior and oblique positions, and the electrocardiogram after a standard two-step exercise test were normal. The average age, weight, and height of the patients were, respectively, 43 years, 201 pounds, and 5 feet, 4 inches (Table I). The weight of the patients was relatively constant except in one who lost 20 pounds.

## METHOD

The three standard leads and the CF leads in the six official positions were recorded in each patient in the sitting position. In twelve patients the CR, CL, unipolar chest (V), and augmented unipolar extremity (aV) leads were also obtained. When the sitting electrocardiogram showed variations from normal, it was repeated in the recumbent position and during inspiration and expiration.

## RESULTS

Eighty-five per cent of the patients showed a mild or moderate degree of left axis deviation in the standard leads; that is, the main deflection of the QRS deviation was directed upward in Lead I and downward in Lead III (Table I). Five patients (15 per cent) showed a $Q_3$ and inverted $T_3$. Six patients (18 per cent) showed inverted $P_3$ in addition to $Q_3$ and inverted $T_3$. In four patients (12 per cent) $P_3$ and $T_3$ were inverted but there was no $Q_3$. Thus, 45 per cent of the patients presented a typical pattern of obesity in Lead III in addition to simple left axis deviation. In two patients (6 per cent) $T_1$ and $T_2$ were less than 1.0 mm. high during one phase of respiration (Fig. 1). A Q wave was not

present in Lead II in any case. One patient showed a small Q wave in Leads $CF_1$, $CF_2$, and $CF_3$ which disappeared with respiration. Another patient revealed a Q wave in Leads $CF_1$ and $CF_2$ which did not vary with respiration. This finding is not unusual normally in these positions in CF leads.

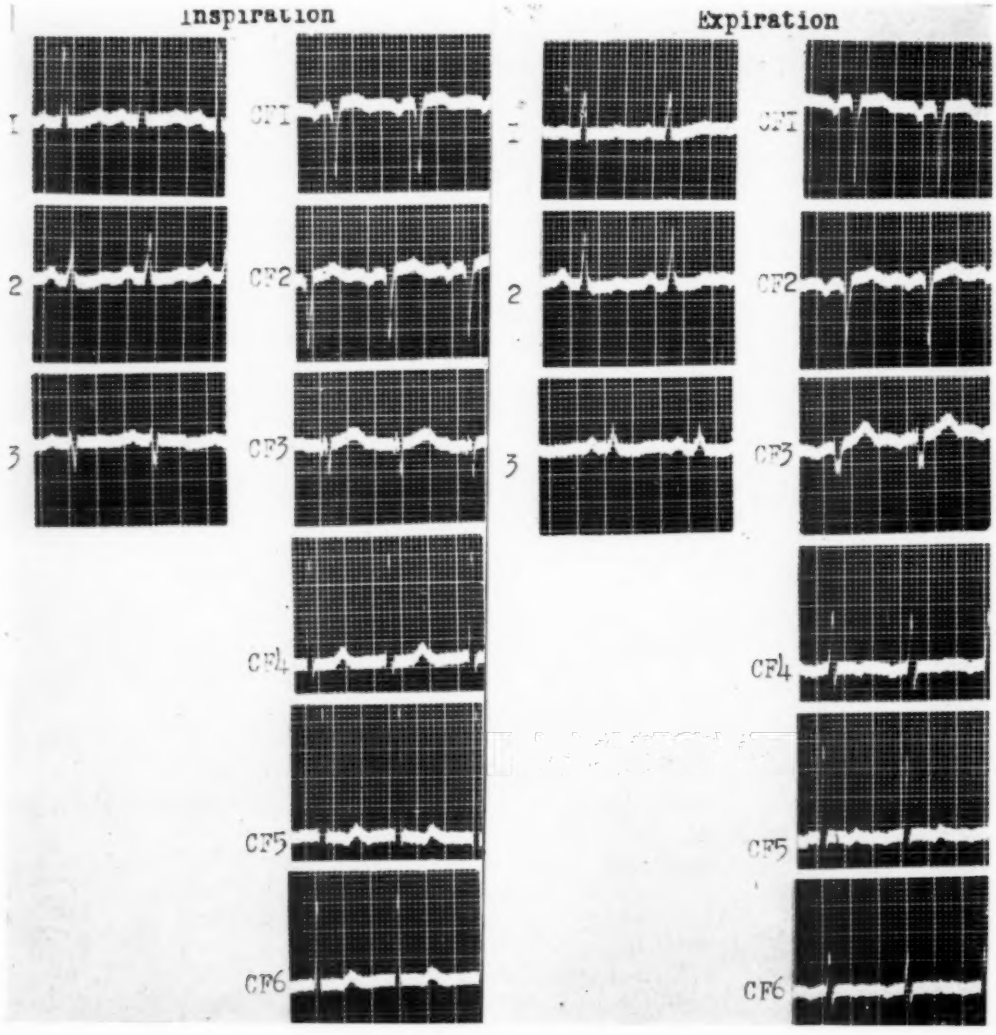



Fig. 1.—S. J., a 43-year-old woman, 5 feet 7 inches tall, weighed 230 pounds. Inspiration: There is left axis deviation, $T_2$ and $T_3$ are low, there is a Q wave in $CF_1$ and $CR_2$, and the T waves is $CF_5$ and $CF_6$ are diphasic. Expiration: There is no axis deviation, $T_1$ is low, and the T waves in $CF_4$ $CF_5$, and $CF_6$ are semi-inverted.

The QRS complex showed a small R wave in Lead $CF_1$ which gradually increased in size until Lead $CF_5$ and then diminished slightly in $CF_6$. The S wave was large in Lead $CF_1$, increased slightly in $CF_2$, and then gradually diminished

in intervening leads to $CF_6$, where it was 1.0 millimeter in height. The average heights of the waves in millimeters were as follows: In $CF_1$, R was 1.7 and S was 7.6; in $CF_2$, R was 2.7 and S was 7.7; in $CF_3$, R was 4.4 and S was 5.6; in $CF_4$, R was 8.3 and S was 4.5; in $CF_5$, R was 9.3 and S was 2.0; in $CF_6$, R was 8.3 and S was 1.0. These figures are considerably lower than those reported in normal subjects[3,4]; in our cases the R wave was almost 50 per cent smaller in Leads $CF_1$, $CF_2$, and $CF_3$ and 33 per cent smaller in $CF_4$ and $CF_5$. Furthermore, the R wave reached its greatest height (transition zone) in Lead $CF_5$ in our series and in $CF_4$ in normal persons. The S wave in Leads $CF_1$, $CF_2$, $CF_3$, and $CF_4$ also was only one-half as large in our series as in normal subjects. The height of the R wave in the V leads approximated that in the CF leads and was also definitely lower than the reported height in normal persons.[15]

Ninety-two per cent of the cases showed T-wave inversion in Lead $CF_1$. This is greater than the incidence of 70 per cent inverted or diphasic T waves found in this position in normal subjects.[3,4] In Leads $CF_2$ and $CF_3$ T was inverted in ten cases (21 per cent), in three of which the inversion varied with respiration. Usually the T wave was upright in expiration and inverted in inspiration (Fig. 1). In Leads $CF_4$ and $CF_5$ T was inverted in four cases (12 per cent), in one of which it varied with respiration, and very low in three cases. In Lead $CF_6$ T was also inverted in four cases (12 per cent), in two of which it varied with respiration, and very low in two cases. The average amplitude of the upright T was 1.2 mm. in $CF_1$, 1.32 mm. in $CF_2$, 1.8 mm. in $CF_3$, 2.2 mm. in $CF_4$, 1.8 mm. in $CF_5$, and 0.88 mm. in $CF_6$. These figures are less than 50 per cent of those reported in normal persons.[3,4] It is noteworthy that in two cases presenting T-wave inversion in the CF leads there was no axis deviation in the standard leads and $P_3$ and $T_3$ were upright.

The CR leads showed upright T waves in all positions except in one patient in whom T was diphasic in Leads $CR_4$, $CR_5$, and $CR_6$. The T wave was always taller than in the CF, CL, and V leads.

The CL leads showed deviation of the T wave in three (25 per cent) of the twelve cases recorded; T was inverted in $CL_1$ and $CL_2$, diphasic or isoelectric in $CL_3$ and $CL_4$, and low in $CL_5$ and $CL_6$. In these three cases the T waves were low in the CF and V leads (Figs. 2 and 3).

The V precordial leads showed low T waves (less than 1.0 mm.) in four cases (33 per cent) but the T wave was not inverted except in Position 1. The average height of T was as follows: in Lead $V_1$, −0.8 mm.; in $V_2$, 2.0 mm.; in $V_3$, 2.2 mm.; in $V_4$, 2.4 mm.; in $V_5$, 2.2 mm.; and in $V_6$, 1.5 millimeters. These values are less than one-half those reported in normal subjects.[15] This was also true of the R wave.

The augmented unipolar extremity leads presented considerable variation of the T wave. In Lead $aV_L$ this wave was high in two cases, normal in two cases, low or isoelectric in seven, and diphasic in one case. In Lead $aV_F$ it was high in five cases, normal in three, low in three, and diphasic in one case. In Lead $aV_R$ the T wave was always inverted except in one case in which it was isoelectric.

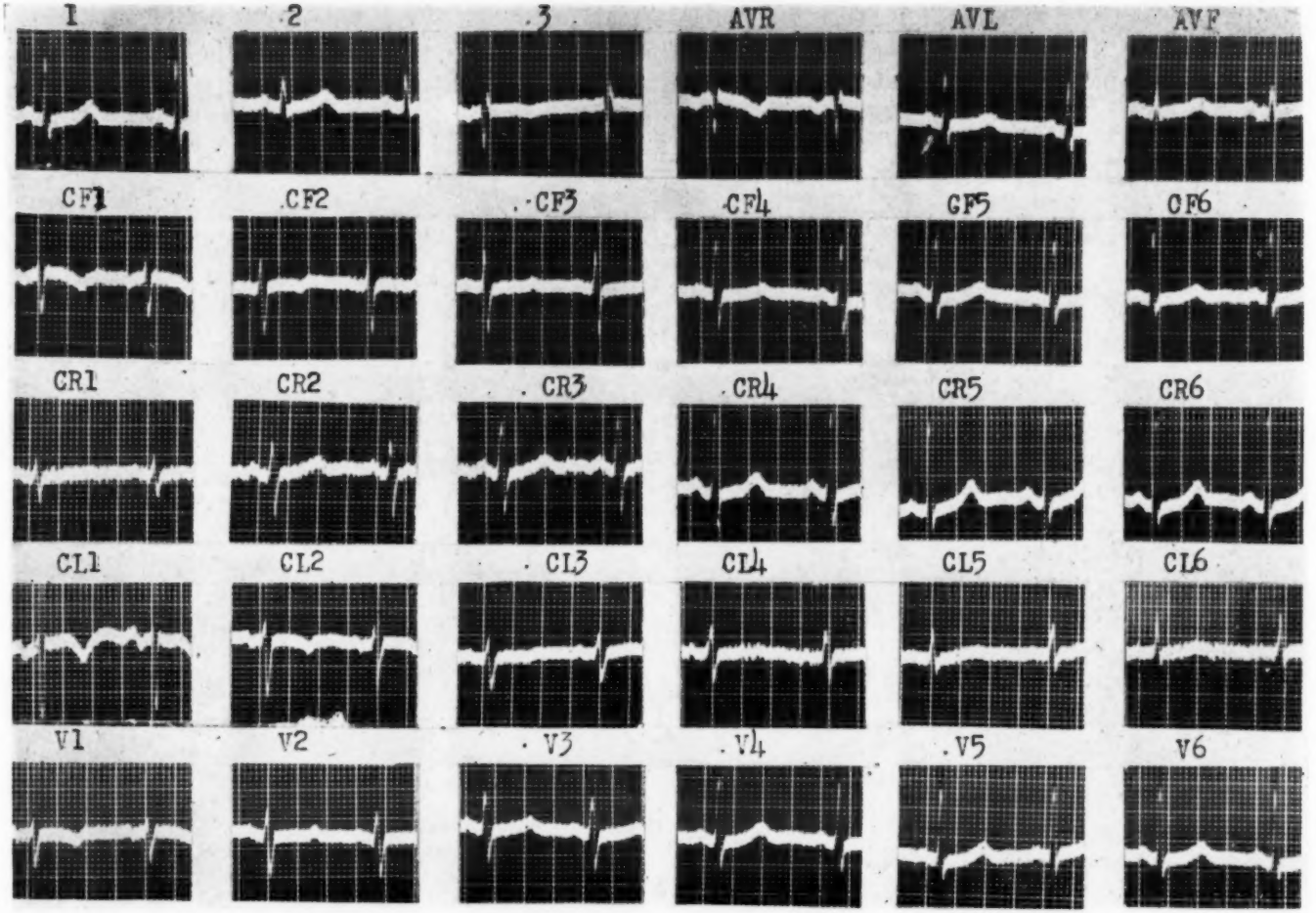



Fig. 2.—R. G., a 46-year-old woman, 5 feet 3 inches tall, weighed 166 pounds. CF leads are within normal limits, showing inverted T wave in Position 1 and diphasic T in Position 2. CL leads show inverted T waves in Positions 1 and 2 and isoelectric T waves in Positions 3, 4, 5, and 6. CR leads are normal. V leads show normal but relatively low T waves in Positions 2 to 6. The T wave in $aV_L$ and $aV_F$ is upright and is greater in $aV_L$. This accounts for the greater distortion of the CL than the CF leads.

Case 17, in which the T wave had originally been inverted in Leads $CF_1$, $CF_2$, $CF_3$, $CF_4$, and $CF_5$, was re-examined five months later after the patient had lost 20 pounds. At this time all of the CF, CR, CL, and V leads were normal (Fig. 4).

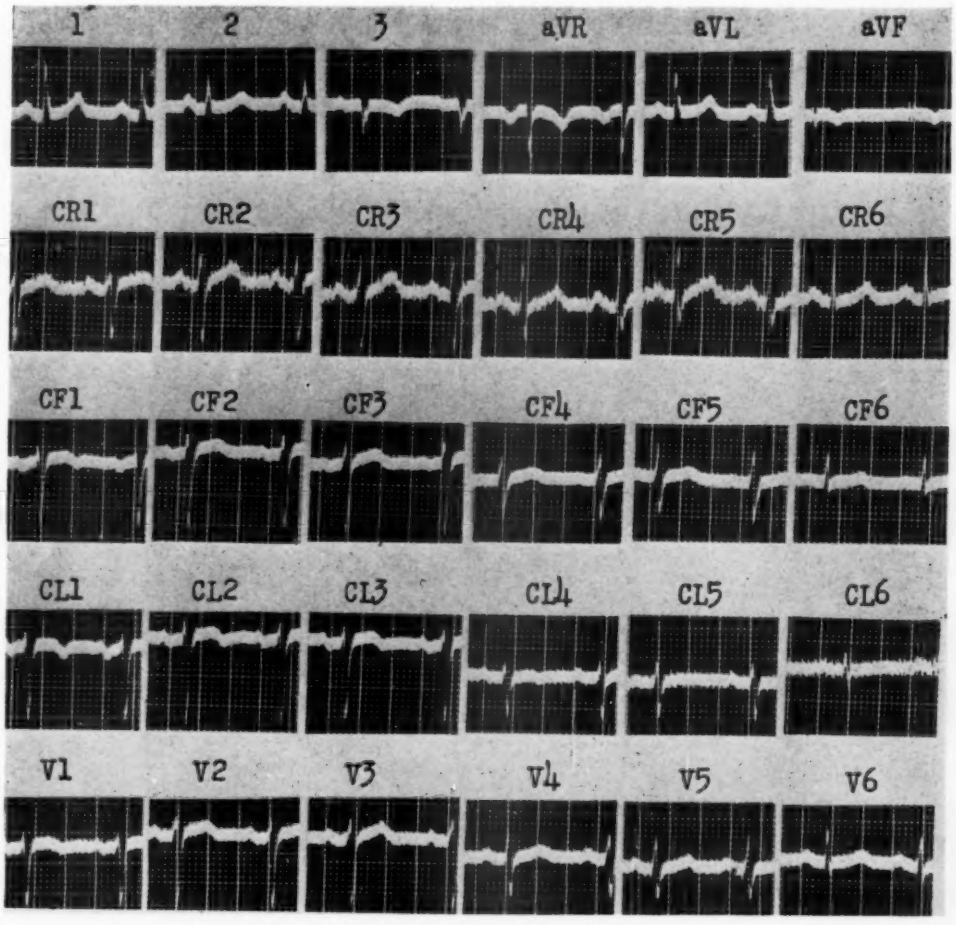
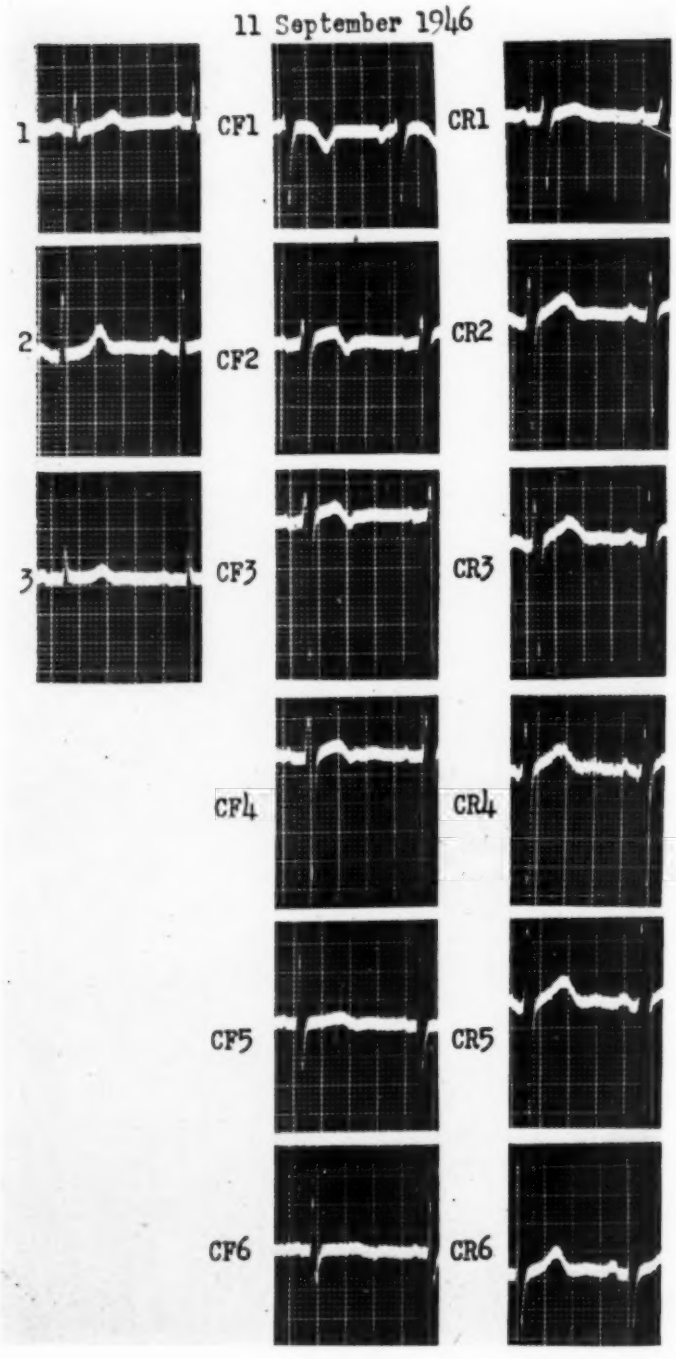



Fig. 3.—L. C., a 41-year-old woman, 5 feet 2 inches tall, weighed 220 pounds. CR leads are normal. CF and V leads are normal and similar, the T waves being relatively low. CL leads show diphasic T waves in Positions 1 to 4 and isoelectric T waves in Positions 5 and 6. Lead $aV_L$ shows upright T wave, accounting for the distortion of CL. In $aV_F$ the T is inverted, but low; therefore, the CF leads are not disturbed.

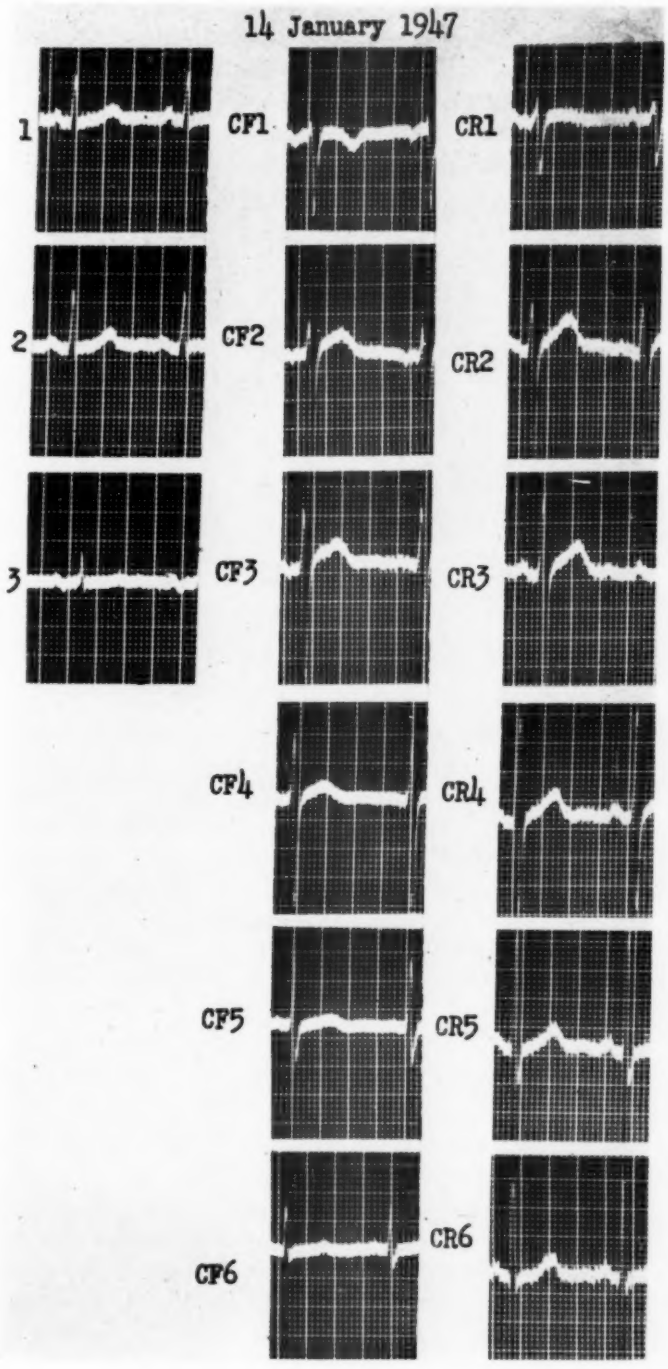
## DISCUSSION

It is apparent that in obesity the T wave, as measured in precordial V leads, is distinctly reduced in amplitude and that, as a result, the influences of the left arm and leg may be great enough to produce further lowering or inversion of the T wave in the CF and CL leads. This does not occur in the CR leads since the T wave is normally negative in Lead $aV_R$ and thus exerts a positive influence on




*A.*

Fig. 4.—E. S., a 50-year-old woman, 5 feet 2 inches tall, weighed 187 pounds. *A*, Sept. 11, 1946: CR leads normal. CF leads show diphasic T waves in all positions. *B*, Jan. 14, 1947, following loss of 20 pounds: CF leads are normal.




*B.*

Fig. 4 (Cont'd).—See opposite page for legend.

the precordial T wave. In Leads $aV_L$ and $aV_F$ the T wave is positive and therefore tends to invert the T wave in the CL and CF leads. Since the precordial T wave is frequently very low in obese persons, the T wave may be isoelectric or inverted in the CL and CF leads even when the T wave in Leads $aV_L$ and $aV_F$ is of normal or low amplitude.

That the T-wave inversion in the CF and CL leads in our cases was not significant is evident from the negative clinical findings, namely, the absence of changes in the electrocardiogram after two-step exercise[16] and the disappearance of the inversion during respiration in one-half the cases and after loss of weight in Case 17. Therefore, the usual interpretation of inversion of the T wave in the CF and CL leads as abnormal does not hold in obese persons; in them V leads are more reliable and should be employed. Our findings thus confirm the suggestion of previous writers[11,13] that distortion effects from the extremity potentials may produce false positives in the CF and CL leads. In addition to the T-wave inversion found in obese persons, we have occasionally observed in other patients a false Q wave in CF leads which was not present in the V leads. It is, therefore, probable that if a single chest lead is to be recorded routinely, the V lead is preferable.

Several authors have suggested that in certain conditions the distortion effects inscribed in the CF and CL leads may be of additional value.[6,13] We have observed a case of coronary occlusion in which a Q wave was present in the CF leads but not in the V leads and occasional cases of acute hemorrhage in which T-wave changes were present only in the CL of CF leads.[17] However, it must be realized that these are distortion effects which are to be evaluated in relation to the unipolar chest and extremity leads. It is our impression that the standard leads and the unipolar chest and extremity leads furnish complete information, but this point requires further investigation in various conditions. It has been stated[12] that CR leads are preferable to the other chest leads. This is true in normal persons, since the CR leads are distorted by the positive influence of the right arm potential and record increased height of the T waves. Thus, these leads do not show the lowering of the T wave seen in obese persons in the other chest leads. However, in abnormal conditions, CR leads may mask T-wave abnormalities.

There are several possible mechanisms by which the amplitude of the precordial T wave is reduced in obese persons. The most likely is clockwise rotation of the heart as a result of elevation of the diaphragm. This causes the right ventricle to face forward and the left ventricle to face backward, thus reducing the precordial electrical potential since the strong left ventricle potential is directed posteriorly. Recently we have clearly observed the influence of the position of the diaphragm on the standard precordial leads in a case of cirrhosis of the liver with ascites (Fig. 5). Prior to removal of the fluid from the peritoneal cavity, the electrocardiogram showed isoelectric T waves in Leads II and III and all chest leads. Following paracentesis the T wave became upright in all leads. Later, post-mortem examination revealed the heart to be normal, and thus the changes in the electrocardiogram were secondary to the alteration in the position of the heart; the heart was situated transversely prior to para-

centesis and normally after it. The disappearance of T-wave inversion in the CF leads in one of our patients following a weight loss of 20 pounds may also be explained in this way. Wallace and associates[18] have suggested that the conducting tissues surrounding the heart are altered when the diaphragm is elevated, resulting in a reduction in the chest potential. A third possible explanation is the thickness of the chest wall in obese persons. However, this factor is not present in pregnancy and ascites in which identical changes occur in the electrocardiogram.

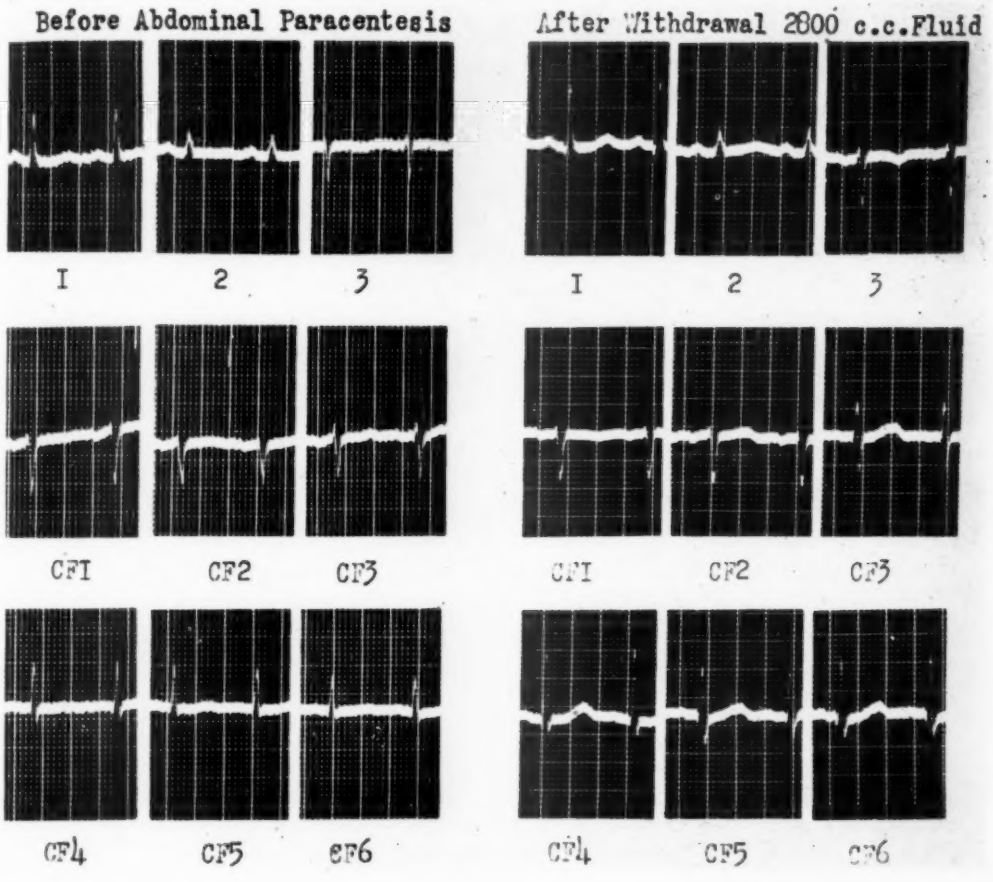



Fig. 5.—J. F., a 50-year-old man with cirrhosis of liver with ascites. Before paracentesis: T waves isoelectric or low in all standard and CF leads. This is the result of elevation of the diaphragm. After paracentesis: T waves are within normal limits.

## SUMMARY

Obesity is often associated with a Q wave and inversion of T in standard Lead III, changes which may simulate myocardial involvement and posterior infarction. The present investigation was undertaken to determine whether significant changes occurred in the chest leads.

In obesity the amplitude of the precordial T wave, as measured in the unipolar (V) leads, is reduced to 50 per cent of normal. However, the T wave was not inverted in the V leads recorded in Positions 2 through 6.

The extremity influences may be great enough to produce significant distortion of the T wave in CF and CL leads. In these leads the T wave was inverted in leads made in Positions 2 and 3 in 20 per cent of the cases of our series, and in leads made in Positions 4, 5, and 6 in 10 to 15 per cent. An inverted T wave in the CF and CL leads obtained from obese subjects is not abnormal. The CR leads show distortion in the direction of normality. This is useful in obesity but may mask T-wave alteration in abnormal conditions.

The diminished height of the precordial T wave in obese subjects is probably the result of elevation of the diaphragm. In support of this view, a case of ascites with T-wave changes in the CF leads is described in which the T waves became normal following paracentesis.

The unipolar chest (V) leads should be employed routinely since they are probably more reliable than the CF, CL, and CR leads.

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# ELECTROCARDIOGRAPHIC CHANGES DURING ANTHIOMALINE TREATMENT OF SCHISTOSOMIASIS

RAMÓN M. SUÁREZ, M.D., DWIGHT SANTIAGO-STEVENSON, M.D., AND FEDERICO HERNÁNDEZ-MORALES, M.D.
SAN JUAN, P. R.

SEVERAL papers have appeared in recent years dealing with the effect of the antimony compounds on the electrocardiogram. Mainzer and Krause[1] observed twelve patients; Magalhaes and Dias[2] studied twenty-one; Tarr,[3] sixty-six; Beaser and Rodriguez Molina[4] reported on twenty-five, and Schroeder, Rose, and Most[5] told of their observations on 100 cases. These investigators used either tartar emetic or Fuadin, or both drugs, and their series included cases of *Schistosoma japonicum* and *Schistosoma mansoni*.

We have chosen for this report twenty cases of a series of over 120 cases of *Schistosoma mansoni*, which have been treated with Anthiomaline. The twenty cases were all male subjects, ranging in age from 12 to 56 years, with an average age of 25.3 years, in whom there was no clinical evidence of cardiovascular disease. Records were taken before treatment was instituted, again after the second injection, after the tenth, two weeks after the last injection, and, in some cases, a final record was taken three months later. Treatment consisted of fifteen injections given intramuscularly in doses of 3.0 c.c. every other day, except Sundays. The electrocardiographic tracings were obtained in the morning hours, usually one hour after the injection, with the patient in the supine position. The three standard leads, the unipolar limb leads, and six precordial leads, using Wilson's central terminal, were taken.

There are three antimony compounds most commonly used in the treatment of schistosomiasis and all are trivalent:

*Tartar emetic* (sodium and potassium tartrate). A freshly made 0.5 per cent solution is given intravenously in doses of 5, 10, and 15 c.c. on the first, third, and fifth days, and subsequently 20 c.c. every other day until a total of 210 c.c. has been given. The entire course of treatment lasts thirty-one days. The amount of the drug administered is 1.45 Gm., which represents 0.522 Gm. of antimony.

*Fuadin* (sodium antimony pyrocatechin sulfonate). A 6.3 per cent solution is given intramuscularly in doses of 1.5 c.c., 3.5 c.c., and 5.0 c.c. on three suc-

From the Department of Medicine, School of Tropical Medicine, San Juan, Puerto Rico.
The Anthiomaline used in this investigation, and in the treatment of over 120 cases of *Schistosoma mansoni*, was generously supplied by Dr. D. F. Robertson, Associated Medical Director of Merck & Co., Inc., Rahway, N. J.
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cessive days, followed by 5.0 c.c. every other day for twelve injections until a total of 70 c.c. has been given. The amount of the drug administered is 4.48 Gm., which represents 0.599 Gm. of antimony.

*Anthiomaline* (antimony salt of lithium anthiomalate). A 6.0 per cent solution is given intramuscularly in doses of 3.0 c.c. every other day, until a total of 60 c.c. has been administered. The amount of the drug injected is 1.35 Gm. Anthiomaline contains 6.9 per cent of lithium and 20 per cent of antimony. One cubic centimeter of the solution is equivalent to 10 mg. of antimony. A full course of treatment, therefore, represents 0.450 Gm. of antimony.

In Mainzer and Krause's[1] series of twelve patients treated with tartar emetic, nine showed electrocardiographic alterations. In three of the nine, the changes were sufficiently abnormal to suggest "suspicion of an altered function of the cardiac muscle." They reported changes in P waves, which turned negative, became lower, or disappeared altogether; changes in T waves, which became lower, isoelectric, or inverted; changes in the S-T and T elements, which became "indistinctly separated and fused with one another"; and a persistent bradycardia during the course of antimony treatment. In their series there was a negative $T_1$ in one case, a negative $T_2$ in another, and a negative $T_3$ in five others. "The electrocardiographic abnormalities," they say, "as well as the bradycardia, are, therefore, considered as resulting from intoxication of the heart muscle through therapeutic antimony administration, though the process in most cases is not clinically evident. In exceptional cases, the condition may result in sudden death, through auricular fibrillation."

Tarr's[3] series of sixty-six patients showed that the electrocardiographic changes were more frequent in those receiving tartar emetic (31 per cent) than in those under Fuadin treatment (7 per cent). Some of the changes, he claims, were so striking that they might have been mistaken for evidences of myocardial damage, but the alterations in the electrocardiogram were limited almost entirely to the T waves. Changes in the P waves, P-R interval, QRS complex, and elevation or depression of the R-T or S-T segment were conspicuously absent, and no disturbances in rhythm were noted. Fig. I of his paper[3] shows negative $T_1$, $T_2$, $T_3$, and $T_4$, which "might easily have been interpreted as evidence of myocardial damage or even coronary occlusion."

Magalhães and Dias[2] reported similar T-wave changes in seven of fourteen of their recorded electrocardiograms. Beaser and Rodriguez Molina[4] found decrease in voltage of the T waves in twenty of their twenty-five patients receiving a course of Fuadin therapy, and recommended that "the course of Fuadin be spaced four or more weeks apart to avoid a cumulative effect upon the myocardium, even though that effect is probably reversible in nature."

Schroeder, Rose, and Most[5] reported an increased amplitude of P waves in Leads II and III in 11 per cent of their cases and a fusion of RS-T segment and T waves in 45 per cent of them. Varying degrees of decrease in amplitude of T waves in all leads with inversion in many cases was reported in 99 per cent of the patients, the changes being more pronounced during tartar emetic than during Fuadin treatment. There was a prolonged Q-T interval in 27 per cent.

They advise that "recent antimony therapy must be considered in evaluating abnormal electrocardiograms found in veterans, and others."

The electrocardiographic alterations have been attributed to the effect of antimony on the heart muscle, although experimentally, in dogs, it has been found that antimony, at least urea stibamine,[6] has no immediate effect upon the electrocardiogram; no lesions were found in the myocardium of dogs which died during the administration of large amounts of antimony.[5] Mainzer and Krause seem to favor vagus stimulation "by narrowing the coronary blood stream" as a possible explanation for antimony effect on the electrocardiogram. They say that there is "marked parallelism between the intensity of the bradycardia and the electrocardiographic changes." On the other hand, Magalhães and Dias attribute the effects of antimony "to dilatation of the capillaries of the coronary circulation with diminution in the effective circulation of the heart." The fact that there is pronounced difference between the effect brought on by tartar emetic and Fuadin and the further fact that the drugs differ also in their antimony values, as well as in the content of sodium and potassium ions, prompted the writers to investigate the electrocardiographic alterations produced by Anthiomaline, which contains no sodium or potassium, but lithium.

The changes induced by a regular course of tartar emetic, which represents the administration of 0.522 Gm. of antimony, are more marked than those observed during a regular course of Fuadin, which represents 0.599 Gm. of antimony. Such changes may point to the possibility that the toxic effect of the antimony molecule is not the sole agent responsible for the changes, unless it has to do with the route of administration. The potassium ions present in tartar emetic (and not in Fuadin) cannot be blamed for the electrocardiographic changes, as it has been shown that hyperpotassemia produces just the opposite change: an increase in T-wave amplitude and lowering and eventual disappearance of P waves.

## RESULTS

*Rhythm, Heart Rate, and* $\hat{A}_{QRS}$.—There were no changes observed in cardiac rhythm, pulse rate, and $\hat{A}_{QRS}$ during Anthiomaline treatment. Table I shows that the number of patients with sinus rhythm and with sinus arrhythmia was

TABLE I. CARDIAC RHYTHM, PULSE RATE, AND $\hat{A}_{QRS}$ BEFORE TREATMENT, AFTER SECOND INJECTION, AND AFTER TENTH INJECTION

| | BEFORE | SECOND RECORD | THIRD RECORD |
|---|---|---|---|
| Sinus rhythm | 11 | 10 | 12 |
| Sinus arrhythmia | 9 | 10 | 8 |
| Pulse rate | | | |
| Minimum | 51 | 55 | 51 |
| Maximum | 81 | 100 | 80 |
| Mean | 61 | 69 | 63 |
| $\hat{A}_{QRS}$ | | | |
| Minimum | + 5.0° | 0.0° | + 8.0° |
| Maximum | +108.0° | +105.0° | +100.0° |
| Mean | + 55.9° | + 54.7° | + 55.0° |

almost equally divided before treatment, after the second injection, and after the tenth injection. There were nine patients with sinus arrhythmia before treatment was started and only eight after the tenth injection. The mean heart rate was 61 per minute before treatment, 69 after the second injection, and 63 after the tenth. There was no bradycardia which could be attributed to therapy. $\hat{A}_{QRS}$ ranged from +5° to +108° before treatment, with an average of +55.9°; from 0° to +105°, with an average of +54.7° after the second injection; and from +8° to +100° after the tenth, with a mean $\hat{A}_{QRS}$ of +55°.

*Limb Leads.—*

*P Waves*: No changes were observed in the amplitude, contour, or duration of the P waves. Table II shows the amplitude of the P waves in Leads I, II, and III before treatment, after the second injection (second record), after the tenth injection (third record), and two weeks after treatment (fourth record). It also includes the number of diphasic, isoelectric, negative, and notched P waves encountered.

TABLE II. AMPLITUDE AND CONTOUR OF P WAVES

| | LEAD I | LEAD II | LEAD III |
|---|---|---|---|
| Before | | | |
| Mean | 0.80 mm. | 1.28 mm. | 0.88 mm. |
| Diphasic± | 0 | 0 | 3 |
| Isoelectric | 0 | 1 | 2 |
| Negative | 0 | 0 | 2 |
| Notched | 2 | 2 | 1 |
| Second record (after second injection) | | | |
| Mean | 0.80 mm. | 1.26 mm. | 0.94 mm. |
| Diphasic± | 0 | 0 | 2 |
| Isoelectric | 0 | 1 | 2 |
| Negative | 0 | 0 | 2 |
| Notched | 2 | 2 | 0 |
| Third record (after tenth injection) | | | |
| Mean | 0.81 mm. | 1.28 mm. | 0.87 mm. |
| Diphasic± | 0 | 0 | 2 |
| Isoelectric | 0 | 0 | 1 |
| Negative | 0 | 0 | 2 |
| Notched | 0 | 2 | 0 |
| Fourth record (two weeks after treatment) | | | |
| Mean | 0.86 mm. | 1.22 mm. | 0.80 mm. |
| Diphasic± | 0 | 0 | 3 |
| Isoelectric | 0 | 0 | 1 |
| Negative | 0 | 0 | 3 |
| Notched | 2 | 2 | 0 |

"Mean" figures represent voltage in millimeters. Other figures represent number of cases.

*P-R Interval*: The duration ranged from 0.10 to 0.18 second both before and during treatment, with an average of 0.15 second.

*QRS Complex*: No change in the amplitude, configuration, or duration of the QRS complex was observed. The mean duration was 0.07 second.

*S-T Segment*: This segment was neither depressed nor elevated during Anthiomaline treatment in Lead I. In Lead II it was found elevated in two instances: in one the elevation was +0.50 mm., originally, but went up to +1.00 millimeter. In Lead III, one patient showed elevation of +1.00 mm. and three others showed a depression of −0.50 mm. and −1.00 mm. following the second injection. The changes in S-T segment were so slight and rare that they could not be considered abnormal findings.

*Q-T Interval*: Table III shows the changes observed in electrical systole in the three standard leads during treatment with Anthiomaline; an increase occurred in the Q-T interval of all leads, but this increase was more pronounced after the tenth injection (third record). Two weeks after cessation of treatment, the Q-T interval had not returned to its original figure.

TABLE III. Q-T INTERVAL BEFORE TREATMENT, AFTER THE SECOND INJECTION, AFTER THE TENTH INJECTION, AND TWO WEEKS AFTER TREATMENT

| | BEFORE (SEC.) | SECOND RECORD (SEC.) | THIRD RECORD (SEC.) | FOURTH RECORD (SEC.) |
|---|---|---|---|---|
| Lead I | | | | |
| Minimum | 0.28 | 0.32 | 0.32 | 0.32 |
| Maximum | 0.36 | 0.40 | 0.40 | 0.40 |
| Mean | 0.340 | 0.345 | 0.357 | 0.351 |
| Lead II | | | | |
| Minimum | 0.32 | 0.32 | 0.32 | 0.32 |
| Maximum | 0.48 | 0.44 | 0.48 | 0.44 |
| Mean | 0.354 | 0.360 | 0.367 | 0.364 |
| Lead III | | | | |
| Minimum | 0.32 | 0.32 | 0.32 | 0.32 |
| Maximum | 0.38 | 0.40 | 0.48 | 0.44 |
| Mean | 0.344 | 0.354 | 0.362 | 0.362 |

In Lead I, thirteen patients showed an increase, three showed a diminution, and four showed no alteration in the Q-T interval. In Lead II, ten patients showed an increase, four showed a diminution, and six suffered no change in the duration of the electrical systole; in Lead III there were thirteen patients with increased Q-T interval, but seven suffered no change in its duration.

*T Waves*: Table IV shows the changes observed in the amplitude and contour of the T waves in the three standard leads. The mean amplitude of the T waves showed a gradual diminution after the second and tenth injections, and a tendency to increase back to its control figure when the fourth record was obtained. Eighteen patients (90 per cent) exhibited a decrease in voltage, and in two records we observed the amplitude of the T wave to increase following the second injection, only to decrease at the tenth.

In Lead I no instance of a negative T wave was encountered either before or during Anthiomaline therapy. In Lead II a negative T wave, present before treatment, became more deeply inverted during treatment. In Lead III there

were two diphasic and three negative T waves before treatment; the same number of diphasic and six negative T waves following the second injection; three diphasic, one isoelectric, and eight negative T waves were present after the tenth injection. Two weeks after treatment, there were only one diphasic, three isoelectric, and four negative T waves in Lead III.

TABLE IV. CHANGES IN THE T WAVES

| | LEAD I | LEAD II | LEAD III |
|---|---|---|---|
| Before | | | |
| Mean | 2.52 mm. | 3.69 mm | 1.48 mm. |
| Diphasic ∓ | 0 | 0 | 2 |
| Isoelectric | 0 | 0 | 0 |
| Negative | 0 | 1 | 3 |
| Second record (after second injection) | | | |
| Mean | 2.43 mm. | 2.84 mm. | 1.23 mm. |
| Diphasic ∓ | 0 | 0 | 2 |
| Isoelectric | 0 | 0 | 0 |
| Negative | 0 | 1 | 6 |
| Third record (after tenth injection) | | | |
| Mean | 2.08 mm. | 2.06 mm. | 1.03 mm. |
| Diphasic ∓ | 0 | 0 | 3 |
| Isoelectric | 0 | 0 | 1 |
| Negative | 0 | 1 | 8 |
| Fourth record (two weeks after treatment) | | | |
| Mean | 2.23 mm. | 2.85 mm. | 1.33 mm. |
| Diphasic ∓ | 0 | 0 | 1 |
| Isoelectric | 0 | 0 | 3 |
| Negative | 0 | 1 | 4 |

In Lead III upright T waves in the control records became negative in four instances; another became diphasic. One which was originally diphasic became negative, and the other diphasic wave underwent no change. Two negative T waves became more pronounced, and the other negative T wave became less pronounced in the third record and isoelectric in the fourth. Most of the changes occurred, therefore, in Lead II, but the alterations observed in the standard leads were never sufficiently pronounced to suggest myocardial or coronary disease.

*Precordial Leads.*—In the chest leads, observations were limited to the P-R interval, duration of the QRS complex, the Q-T interval and the S-T segment, and to a study of the P and T waves in the six precordial leads. Table V shows that there were no alterations in the P-R interval or in the duration of the QRS complex.

*P Waves*: The small P waves in the precordial leads normally diminish in amplitude when the exploring electrode is moved to the left side of the chest. The mean amplitude in this series being 0.359 mm. in Lead $V_1$ and only 0.138 mm. in Lead $V_6$, there is, consequently, an increased number of isoelectric P waves in the latter lead (six cases with none in $V_1$). The mean amplitude of the

P waves was slightly less in Leads $V_1$ and $V_2$, but somewhat higher in the other four precordial points after the second injection (second record in Table V). After the tenth injection (third record), the amplitude of the P waves increased slightly in leads made at precordial Positions 1, 2, 3, and 5, but diminished in leads made at Positions 4 and 6. When the fourth record was taken, in none of the cases had the P waves returned to its control figure. The most pronounced changes in amplitude and contour of the P waves were, of course, observed in Lead $V_1$.

TABLE V. CHANGES IN THE P WAVES IN PRECORDIAL LEAD

| | $V_1$ | $V_2$ | $V_3$ | $V_4$ | $V_5$ | $V_6$ |
|---|---|---|---|---|---|---|
| Before | | | | | | |
| Mean | 0.359 mm. | 0.302 mm. | 0.209 mm. | 0.252 mm. | 0.189 mm. | 0.138 mm. |
| Isoelectric | 0 | 0 | 2 | 1 | 3 | 6 |
| Diphasic± | 1 | 0 | 0 | 0 | 0 | 0 |
| Negative | 1 | 0 | 0 | 0 | 0 | 0 |
| Second record (after second injection) | | | | | | |
| Mean | 0.330 mm. | 0.288 mm. | 0.214 mm. | 0.251 mm. | 0.215 mm. | 0.170 mm. |
| Isoelectric | 3 | 3 | 5 | 2 | 3 | 6 |
| Diphasic± | 2 | 0 | 0 | 0 | 0 | 0 |
| Negative | 0 | 0 | 0 | 0 | 0 | 0 |
| Third record (after tenth injection) | | | | | | |
| Mean | 0.446 mm. | 0.324 mm. | 0.287 mm. | 0.204 mm. | 0.201 mm. | 0.133 mm. |
| Isoelectric | 2 | 0 | 0 | 2 | 4 | 6 |
| Diphasic± | 1 | 0 | 0 | 0 | 0 | 0 |
| Negative | 0 | 0 | 0 | 0 | 0 | 0 |
| Fourth record (two weeks after treatment) | | | | | | |
| Mean | 0.389 mm. | 0.330 mm. | 0.289 mm. | 0.184 mm. | 0.155 mm. | 0.120 mm. |
| Isoelectric | 1 | 1 | 1 | 3 | 2 | 5 |
| Diphasic± | 3 | 0 | 0 | 0 | 0 | 0 |
| Negative | 0 | 0 | 0 | 0 | 0 | 0 |

P-R interval = 0.10 – 0.18 sec. Av. 0.152 sec.
QRS duration = 0.04 – 0.10 sec. Av. 0.083 sec.

*T Waves*: The amplitude and contour of the T waves of the precordial Leads appear in Table VI. There was a definite decrease in amplitude of the T waves observed during Anthiomaline treatment with a tendency to return to the control figures two weeks after treatment.

Before treatment, there were five diphasic T waves in Lead $V_1$, one in Lead $V_2$, and one in Lead $V_3$, and two negative T waves in Lead $V_1$ and one in Lead $V_2$.

After the second injection of Anthiomaline there were three negative T waves in $V_1$, one in $V_2$, and one in $V_3$; the diphasic T waves suffered no alterations, except that one appeared in Lead $V_1$. After the tenth injection, the number of negative T waves increased to five in $V_1$, one in $V_2$, one in $V_3$, two in $V_4$, one in $V_5$, and one in $V_6$. Two weeks after treatment, there were six negative T waves in Lead $V_1$, one in $V_2$, one in $V_3$, and two in Lead $V_4$.

TABLE VI. CHANGES IN T WAVES IN PRECORDIAL LEADS

| | $V_1$ | $V_2$ | $V_3$ | $V_4$ | $V_5$ | $V_6$ |
|---|---|---|---|---|---|---|
| Before | | | | | | |
| Mean | 1.55 mm. | 3.15 mm. | 3.60 mm. | 3.56 mm. | 3.30 mm. | 2.55 mm. |
| Diphasic± | 5 | 1 | 1 | 0 | 0 | 0 |
| Negative | 2 | 1 | 0 | 0 | 0 | 0 |
| Second record (after second injection) | | | | | | |
| Mean | 1.58 mm. | 2.79 mm. | 3.01 mm. | 2.88 mm. | 2.66 mm | 2.02 mm. |
| Diphasic± | 5 (1∓) | 1 | 0 | 0 | 0 | 0 |
| Negative | 3 | 1 | 1 | 0 | 0 | 0 |
| Third record (after tenth injection) | | | | | | |
| Mean | 1.35 mm. | 1.93 mm. | 2.54 mm. | 2.26 mm. | 2.0 mm. | 1.64 mm. |
| Diphasic± | 5 | 1 | 1 | 0 | 0 | 0 |
| Negative | 5 | 1 | 1 | 2 | 1 | 1 |
| Fourth record (two weeks after treatment) | | | | | | |
| Mean | 1.37 mm. | 2.35 mm. | 3.02 mm. | 2.63 mm. | 2.32 mm. | 1.98 mm. |
| Diphasic± | 4 | 4 | 1 | 0 | 0 | 0 |
| Negative | 6 | 1 | 1 | 2 | 0 | 0 |

A boy, 12 years of age, showed negative T waves in $V_1$, $V_2$, $V_3$, and $V_4$ following the tenth injection when the control record showed negative T waves only in $V_1$ and $V_2$ (Fig. 1). A man, 24 years of age, who originally showed only diphasic T waves in $V_1$, showed negative T waves at all six precordial points after the tenth injection (Fig. 2).

The amplitude of the T waves decreased during Anthiomaline treatment in eighteen of the twenty patients (90 per cent). In four cases, however, an increase in amplitude of the T waves after the second injection was found. In one case, in Lead $V_3$, the T waves, two weeks after treatment, were 6.0 mm. when the control amplitude had been only 3.25 mm., having gone down to 1.50 mm. during therapy; also in another case the amplitude of the T wave was higher after (3.75 mm.) than before (2.25 mm.) treatment.

*The S-T Segment*: This portion of the ventricular complex was found on the isoelectric line in 60 per cent of the cases and from 0.5 to 1.0 mm. above the isoelectric line in 40 per cent. When it was above the isoelectric line, the control record was also slightly elevated. In Lead $V_1$ only four patients showed elevation. In Lead $V_6$ only one showed elevation. These were normal findings.

*Q-T Interval*: In the precordial leads, the electrical systole suffered a slight prolongation, similar to that observed in the three standard leads. For the sake of brevity, we are giving the figures for only Lead $V_5$ (Table VII).

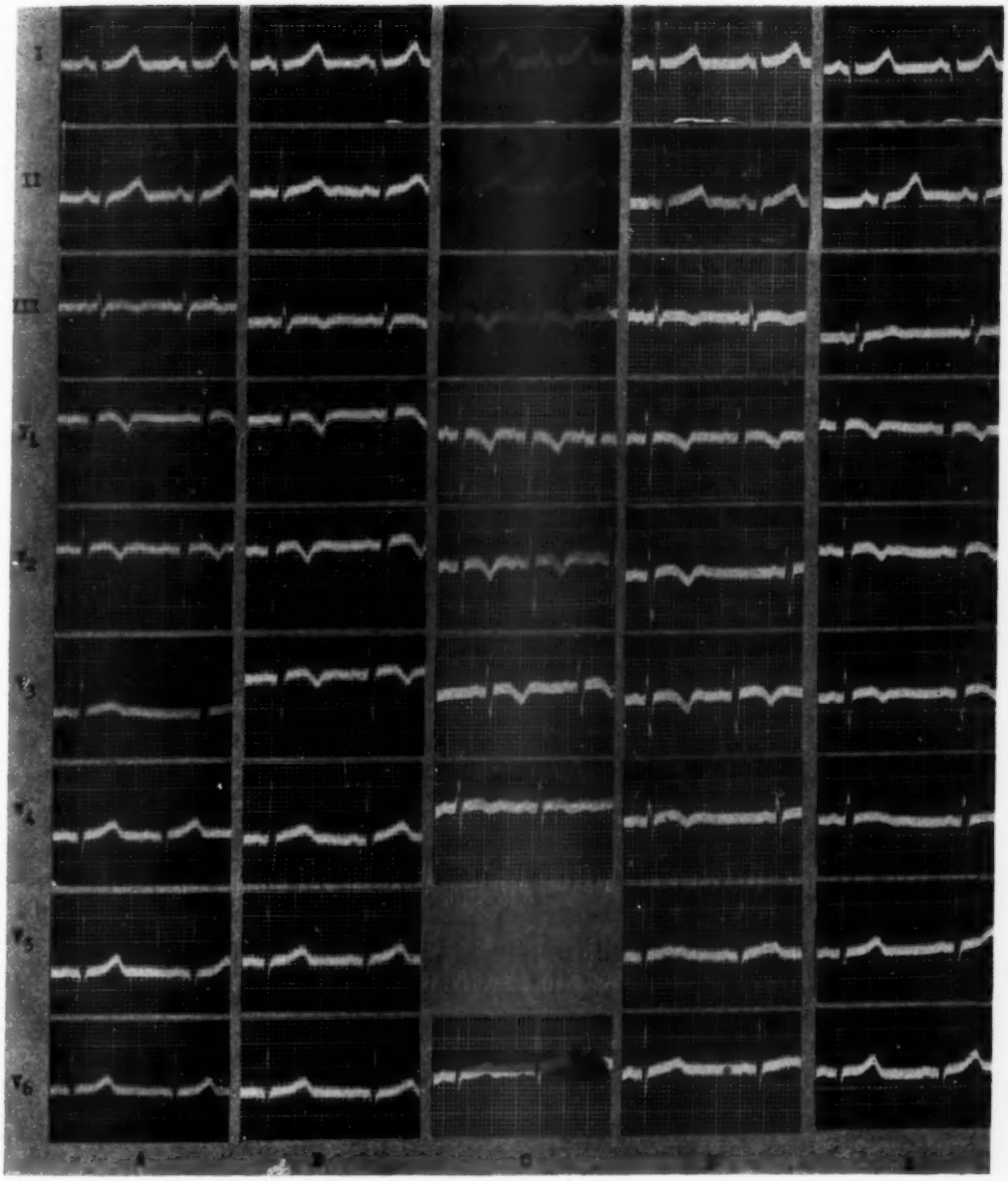


Fig. 1.—B. P. (Case 2025), 12 years of age. *A*, control record; *B*, after second injection; *C*, after tenth injection; *D*, two weeks after treatment; *E*, three months after treatment.

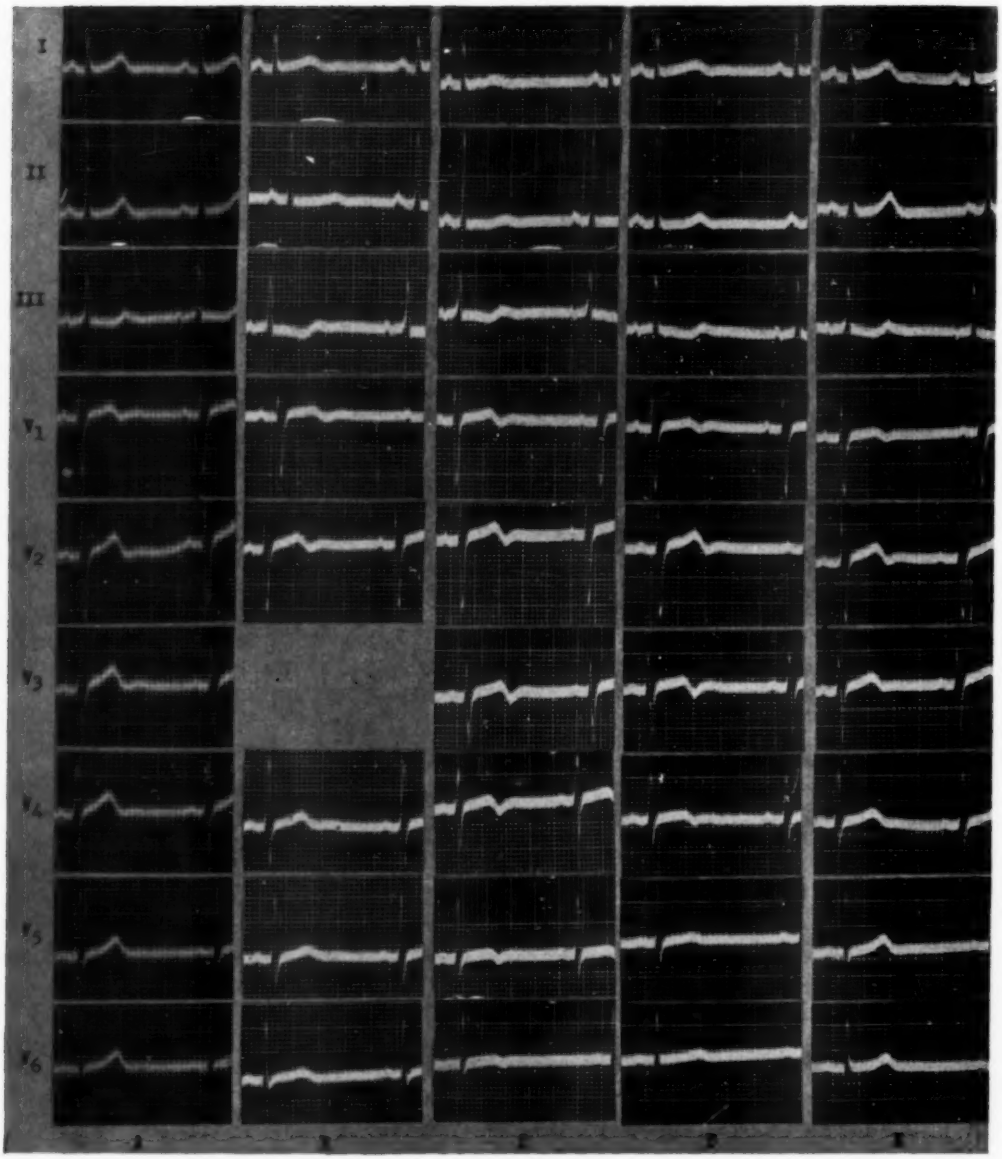


Fig. 2.—J. S. (Case 7080), 24 years of age. *A*, control record; *B*, after second injection; *C*, after tenth injection; *D*, two weeks after treatment; *E*, three months after treatment.

TABLE VII. Q-T INTERVAL IN $V_5$ BEFORE TREATMENT, AFTER SECOND INJECTION, AFTER TENTH INJECTION, AND TWO WEEKS AFTER TREATMENT

| | BEFORE (SEC.) | AFTER SECOND INJECTION (SEC.) | AFTER THIRD INJECTION (SEC.) | TWO WEEKS AFTER TREATMENT (SEC) |
|---|---|---|---|---|
| Minimum | 0.32 | 0.30 | 0.32 | 0.32 |
| Maximum | 0.38 | 0.40 | 0.44 | 0.38 |
| Mean | 0.348 | 0.351 | 0.358 | 0.356 |


## SUMMARY

1. Electrocardiographic changes observed during Anthiomaline treatment of schistosomiasis were limited to the T waves and to the Q-T interval.

2. A decrease in amplitude of the T waves was present in 90 per cent of the cases. In the standard leads, the changes in the T waves were so slight that they could not, per se, be considered to be of pathologic significance. A negative $T_1$ was not encountered.

3. The changes in the T waves were more pronounced in the precordial leads. A boy, 12 years of age, showed negative T waves in Leads $V_1$, $V_2$, $V_3$, and $V_4$, following the tenth injection, when the control record showed negative T waves only in Leads $V_1$ and $V_2$; and a man, 24 years of age, who originally showed only a diphasic T wave in Lead $V_1$, showed negative T waves after the tenth injection in all six precordial leads.

4. With negligible or no changes in pulse rate, there was found a prolonged Q-T interval in about 50 per cent of the cases, more marked after the tenth injection in both standard and precordial leads.

5. It appears that the electrocardiographic changes which occur during Anthiomaline treatment of schistosomiasis are less pronounced than those observed during treatment with tartar emetic, and compare favorably with the changes induced by Fuadin.


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# Clinical Reports

## BACTERIAL ENDOCARDITIS

### Report of a Case in Which a True Musical Diastolic Murmur Appeared and Disappeared

Richard C. Cecil, M.D., Carl P. Parker, Jr., M.D., and
William B. Porter, M.D.
Richmond, Va.

A CASE report of a patient with acute bacterial endocarditis with postmortem examination is presented. It is deemed worthy of reporting for the following reasons: (1) With the use of the new antibiotics in the treatment of various forms of bacterial endocarditis, there has been renewed interest in these diseases. (2) A survey of English literature for the past twenty years reveals no case showing the appearance and disappearance of a true musical murmur. This case shows this, and there is available a satisfactory physiologic and pathologic explanation. (3) The effect that a mechanical heart defect plays in precipitating heart failure is re-emphasized and the improvement of heart failure which accompanies improvement in the valve defect is clearly shown.

#### CASE REPORT

The patient, a 61-year-old white man, was admitted to the hospital on Jan. 21, 1946. His chief complaints were anorexia and loss of weight. These symptoms had been present for approximately three months. Fatigue had been present from the onset of the present illness and breathlessness, for only a few days prior to hospital admission. On the morning of admission, slight swelling of the ankles was apparent.

The past history was one of good health, with no serious illnesses or accidents. There was no history of rheumatic fever or syphilis.

*Physical Examination.*—The temperature was 100.8° F.; pulse rate, 85; respirations, 20 per minute; and blood pressure, 170/80. The patient was a poorly nourished, but well-developed man, who was in no acute distress. A few moist râles were heard at the base of each lung. The heart was enlarged. There was a diastolic murmur heard best over the aortic area and along the left sternal border and a diastolic murmur at the apex, with a thrill, diastolic in time, at the aortic valve area. The liver was palpable 3.0 cm. below the right costal margin. There was a 1 plus pitting edema of both ankles. The prostate was moderately enlarged, firm, smooth, and nontender.

Laboratory studies on admission showed a urine with specific gravity of 1.013, 1 plus albumin, 65 to 75 white blood cells, and 2 to 4 red blood cells per high-power field, and rare hyaline casts.

From the Department of Medicine, Medical College of Virginia, Richmond, Va.
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The blood showed 3,280,000 red blood cells, hemoglobin of 60 per cent, 12,100 white blood cells, 93 per cent polymorphonuclear leucocytes, 3 per cent lymphocytes, and 4 per cent monocytes. The nonprotein nitrogen was 60 mg. per cent. A blood culture taken on admission was reported to be positive for nonhemolytic streptococci after three days of culture.

One day after admission and several hours following a 500 c.c. transfusion of citrated blood, the patient developed severe pulmonary edema, for relief of which, the removal of 500 c.c. of blood was required. A high-pitched, loud, musical diastolic murmur was then noticed which could be heard at any point on the patient's chest (anterior or posterior), over the upper abdomen, and over the upper humerus. This was confirmed by stethogram (Fig. 1). He remained in severe cardiac failure and required digitalization, oxygen, aminophyllin, and morphine. At this time, the blood pressure changed gradually from 170/70 to 150 to 160/0 to 30 (Fig. 2), and the nonprotein nitrogen rose to 100 mg. per cent. Penicillin, 15,000 units every three hours, was started and increased to 40,000 units every two hours two days later.

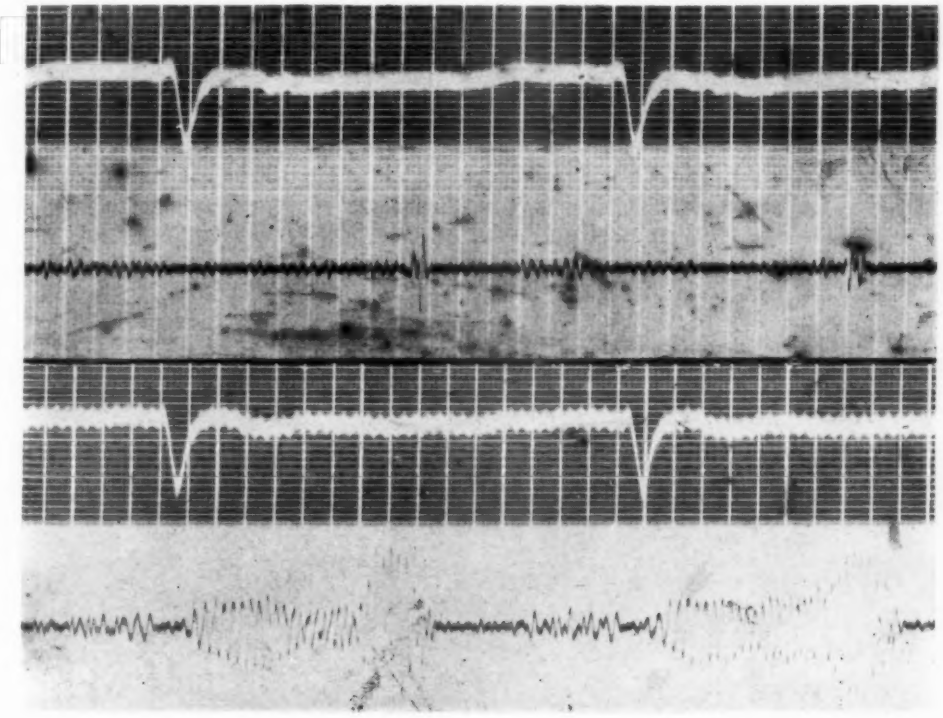

Fig. 1.—Stethoscopic electrocardiograms. Upper, musical murmur present, Jan. 25; lower, musical murmur absent, Feb. 21.

Failure was marked and continued. Severe dyspnea and orthopnea, distended neck veins, basal lung moisture, enlargement of the liver, and ankle edema were present. On Feb. 11, 1946, twenty days after admission, the high-pitched, musical murmur gradually disappeared; the change was confirmed by a stethogram (Fig. 1). The symptoms and phenomena of cardiac failure rapidly diminished. The nonprotein nitrogen was reduced to 30 mg. per cent from a previous level of 100 mg. per cent.

By February 19, the patient was able to be up in a wheel chair. The improvement was thought to be due to a healing of the aortic valve; however, positive blood cultures for the same organism, a gram-positive gamma streptococcus, were still obtained. The laboratory reported

the organism to be penicillin resistant, but inhibited by 5 units of penicillin per milliliter, so that the dosage was increased to 80,000 units every two hours.[3] The blood pressure no longer showed the wide pulse pressure but had gradually returned to 125/70 (Fig. 2). Sulfadiazine was started and penicillin continued, but in spite of this therapy, repeated blood cultures were reported to be positive for the same organism.

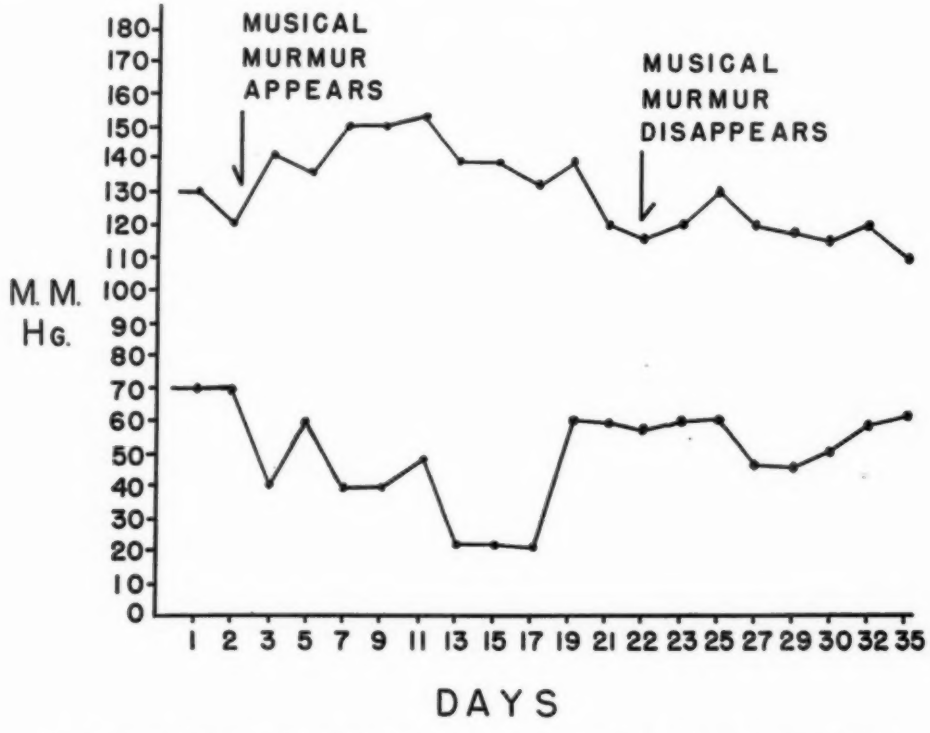


Fig. 2.—Blood pressure readings showing wide pulse pressure with musical murmur present.

On February 25, the patient's clinical condition was worse. There was a low-grade fever, 98 to 101.4° F., congestive failure had gradually but steadily increased, and there was a progressive downward course. Death occurred on April 2, 1946, seventy days after admission. Penicillin, 39,217,000 units, had been administered.

*Post-Mortem Examination.*—The findings pertaining to this report were in the heart. Elsewhere, the findings were: severe pulmonary congestion with edema, moderate chronic passive congestion of the liver, a solitary splenic abscess of metastatic origin (septic infarct), benign prostatic hypertrophy, and moderate atherosclerosis of the aorta. The kidneys were of normal size and sections showed patchy areas of fibrosis of glomeruli and destruction of tubules.

The heart was grossly enlarged, weighing 700 grams. The pericardium was normal. The myocardium was firm and thickened. The pulmonary and tricuspid valves were essentially normal. The leaflets of the aortic valve were involved in a bacterial process, with vegetations which averaged 5.0 mm. in their greatest diameter. They were firmly attached and nonfriable. The posterior and right cusps were perforated along the inferior margin, the perforations measuring 2.0 to 3.0 mm. in diameter (Fig. 3). Each perforation was blocked by a large bacterial vegetation which occluded the opening in the valve cusps produced by the perforation. The endocardium of the anterior leaflet of the mitral valve was involved by one large vegetation. The chordae

tendineae of this valve were shortened but not thickened. Neither valve showed gross pathologic evidence of previous scarring. The coronary ostia were patent and the arteries were functional throughout.

Microscopic study of the heart revealed edema of the endocardium around the aortic cusps. The vegatations of the aortic valve were shown to be composed of platelets, fibrin, polymorphonuclear leucocytes, and lymphocytes. Clusters of bacteria were seen on the outer surfaces and Gram's stain showed these to be gram-positive cocci.

Fig. 3.—Photograph of heart showing perforations of aortic valve.

## DISCUSSION

In the case which has been presented, symptoms were of approximately five and one-half months' duration. This prolonged course, with the marked improvement after the disappearance of the musical murmur, led us to believe that recovery was taking place. The repeatedly positive blood cultures and the subsequent course showed that this optimism was unjustified. Undoubtedly, the large dosage of penicillin, 39,217,000 units, inhibited the progression of the disease and allowed it to be of longer duration than usual.

The most interesting clinical observation was the appearance of the musical murmur, and, later, its disappearance, together with the effect that these changes had upon the clinical course. Cardiac function was fair until the development of the perforations of the leaflets of the aortic valve, which caused the murmur. Immediately after the perforation, the patient developed severe cardiac failure. The effect of sudden perforation of an aortic valve leaflet was previously ob-

served by Porter[4] in a case of gonococcal endocarditis in which the patient developed a musical murmur and perforation of the aortic valve while he was being examined. Our patient, fortunately, lived longer so that we were able to observe him at greater length. As long as the musical murmur was present, cardiac failure was irreversible, with the severity of failure being definitely related to the pulse pressure. With the disappearance of the musical quality of the diastolic murmur there was lessening of the pulse pressure and improvement, which was probably related to lessening of aortic insufficiency due to plugging of the perforations by vegetations.

## SUMMARY

A case of acute bacterial endocarditis due to a gamma (nonhemolytic) streptococcus, in which death occurred in spite of massive penicillin therapy, has been reported. A true musical diastolic murmur, caused by perforation of two cusps of the aortic valve, occurred during the course of the disease. This was accompanied by severe congestive heart failure. With the disappearance of the musical quality of the aortic diastolic murmur, there was a prompt lessening of the pulse pressure and a progressive improvement in the symptoms and the degree of heart failure. What was interpreted as evidence of improvement was in reality increase in the size of vegetations on the aortic valve which produced occlusion of the perforations of the valve.

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# CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION FOLLOWING CHOLECYSTECTOMY FOR RELIEF OF ANGINAL PAIN IN A PATIENT WITH CHOLELITHIASIS

OSCAR ROTH, M.D.*
NEW HAVEN, CONN.

THE inter-relationship between the pain caused by diseases of the coronary arteries and the biliary tract is well recognized. Miller[1] believes that this inter-relationship is due to a common autonomic reaction and that a common afferent pathway is brought into action when the referred pain of coronary artery disease simulates that of gallbladder and biliary duct disease, and vice versa.

In experimental distention of the human gallbladder, changes in heart rate, disturbances in rhythm, and changes of the T waves have been found.[2] Buchbinder[3] found that in icteric animals a reflex mechanism from distended biliary passages caused cardiac arrhythmias and heart block, probably by way of the vagus nerve. Further, Gilbert[4] has shown both experimentally and clinically that stimuli originating in the gallbladder or in the bile ducts may cause a decrease in the coronary blood flow, which results in a disproportion between blood supply and blood needs similar to those which occur when intrinsic anatomic changes take place in the coronary vessel wall. The belief has been expressed by Owen[5] that a heart which is already damaged by coronary sclerosis might, in the presence of disease of the biliary tract, show electrocardiographic abnormalities on much less provocation than would a normal heart. Patients with organic heart disease, particularly patients with angina pectoris, who were greatly benefitted by the removal of the diseased gallbladder, were reported by Babcock.[6,7] In addition, Hamburger and Strauss[8] described patients whose cardiac arrhythmias disappeared, and whose electrocardiograms became normal following cholecystectomy.

In the experience of Ravdin,[9] the risk incurred in operating upon such patients is not great provided they receive proper care before and during operation. A number of patients who had been unsuccessfully treated for severe anginal pain by competent internists became symptom free following cholecystectomy performed by Verdi.[10] White,[11] however, warns that cholecystectomy may occasionally be followed by coronary occlusion with myocardial infarction.

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From the Medical Service, St. Raphael Hospital and the Heart Clinic, Grace-New Haven Community Hospital, New Haven, Conn.

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*Clinical Instructor in Medicine, Yale University; Attendant of the Heart Clinic, Grace-New Haven Community Hospital.

In the case herein reported, this complication occurred, but remained unrecognized for twelve days.

## CASE REPORT

H. P., a man, 49 years of age, was admitted to a general hospital in June, 1946, with a four-month history of substernal pain and slight dyspnea, brought on by heavy exercise. The substernal pain on exertion occurred from five to six times daily, but at times was absent for several days. It did not directly radiate but it was associated with severe pain in one or both elbows, and with dizziness. No perspiration or pallor was present during these attacks. The pain lasted from one to ten minutes if untreated, but responded promptly to nitroglycerin. The patient noticed that he became tired easily. He complained also of an abdominal fullness and slight epigastric pain, which he described as gas pain, following meals. There was no history of biliary colic, jaundice, or clay colored stools.

The past history was negative, except for influenza. The patient smoked thirty cigarettes daily and drank alcoholic beverages moderately and occasionally.

On physical examination, the patient did not appear to be acutely or chronically ill; he was slightly undernourished, and looked older than his stated age. No cyanosis was present. The ocular fundi showed no abnormalities. The blood pressure was 110/60; the pulse rate was 65 per minute and regular. His temperature was 98.4° Fahrenheit. Heart and lungs were normal to percussion and auscultation. The examination of the abdomen revealed no masses, tenderness, or rigidity. The pulse of the dorsalis pedis artery was easily palpable bilaterally.

The white blood count was 7,800 and the hemoglobin was 90 per cent. The differential count showed 60 per cent neutrophiles, 39 per cent lymphocytes, and 1 per cent monocytes. The Kahn test was negative. Examination of the urine revealed nothing significant. The clotting time was 1.5 minutes (capillary method).

Roentgenographic examination of the chest revealed normal heart and lungs, and no evidence of diaphragmatic hernia in the Trendelenburg position. Cholecystograms following administration of Priodax tablets showed normal gallbladder function but numerous small choleliths.

The resting electrocardiogram was within normal limits. An exercise tolerance test brought out signs of coronary insufficiency manifested by low T waves in Lead I and diphasic T waves in Lead $CF_4$, three minutes following exercise (Fig. 1).

In view of these findings, it was thought that the patient's cardiac complaints could be aggravated by the coexisting cholelithiasis. It seemed probable that cholecystectomy might improve the patient's cardiac status, despite the fact that the biliary symptoms were minimal. Consequently, cholecystectomy and appendectomy were performed on June 7, 1946. The patient was anesthetized with 9 c.c. of sodium pentothal and 4 ounces of ether. The operation required two hours, but no serious difficulties were encountered. Dense adhesions were found around the gallbladder, but the common duct was probed and found to be patent. The thickened gallbladder was 8.0 cm. long and 4.0 cm. wide and contained about 100 small, dark brown, irregular stones. The pathologic diagnosis was chronic cholecystitis with cholelithiasis, and normal appendix.

The postoperative course was reported by the surgical staff as uneventful. The patient was allowed to be out of bed on the first postoperative day. He resumed normal activity on the ninth postoperative day, and on the twelfth postoperative day he was discharged from the surgical service. On this day he walked about one-half mile without considerable discomfort. Although the patient had no immediate complaints except fatigue, an electrocardiogram showed signs of a recent anterior myocardial infarction (Fig. 2). A white blood count was 7,400. The corrected sedimentation time was 39 mm. in one hour. The clotting time was 2 minutes.

On more careful questioning, the patient acknowledged that on the first postoperative day he had experienced upper abdominal pain which was associated with pain in both elbows. The pain in the abdomen and left elbow lasted for the entire day, that in the right elbow, for three days. There was no pain in the shoulders or in the upper arms. Symptoms were not severe enough to require narcotics nor to confine the patient to bed.

As soon as the abnormal electrocardiogram was seen, the patient was placed on strict bed rest. The subsequent course was uneventful. Four months after the operation the patient felt well, and complained only of exertional dyspnea and occasional chest pain. Electrocardiograms taken at intervals showed persisting signs of anterior myocardial infarction.

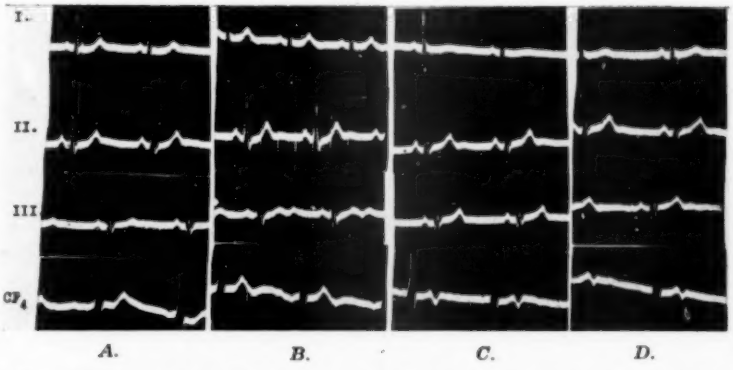


Fig. 1.—Exercise tolerance test shows signs of coronary insufficiency. The upright $T_1$ becomes almost isoelectric; the upright T of $CF_4$ becomes diphasic three minutes after exercise. *A*, Resting recumbent on June 2, five days prior to operation; *B*, immediately after exercise; *C*, three minutes after exercise; *D*, eight minutes after exericse.

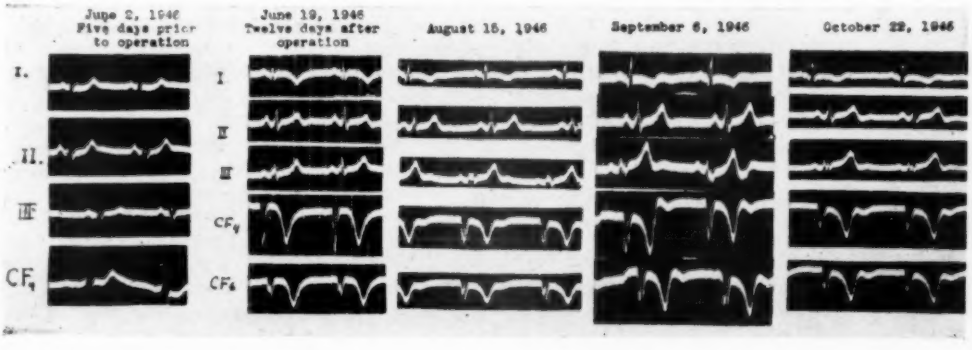


Fig. 2.—Electrocardiograms before and after cholecystectomy. The first electrocardiogram after operation was taken June 19, 1946, for a routine check-up. No myocardial infarct was suspected.

## DISCUSSION

It is a matter of pure conjecture whether the myocardial infarction was precipitated by the trauma of the operation or whether it would have occurred without operation. It is of importance, however, that the symptoms of myocardial infarction were mistaken for wound pain and that the patient was allowed to leave his bed one day after the operation, the day on which myocardial infarction probably occurred. Considering the fact that, on one hand, the most valuable treatment of myocardial infarction is prolonged bed rest and

that, on the other hand, the trend of modern surgery is toward short periods of bed rest, a mistake of this kind could, theoretically at least, be of great consequence.

Routine postoperative electrocardiograms on every patient with known coronary artery disease prior to mobilization and on every patient in whom there is severe abdominal pain following operation could greatly reduce the danger of overlooking a myocardial infarct.

## SUMMARY

1. A case of anterior myocardial infarction immediately following cholecystectomy and appendectomy in a patient with cholelithiasis and coronary artery disease is reported.

2. The primary purpose of the operation, in this case, was the relief of anginal pain by the removal of extracardiac causes of the pain.

3. The pain of myocardial infarction was mistaken for postoperative wound pain.

4. Routine postoperative electrocardiograms taken in such patients may prevent such errors.

The author gratefully acknowledges the advice of Dr. W. F. Verdi and Dr. H. M. Marvin in making this report.

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# Abstracts and Reviews

## Selected Abstracts

**Siegmund, O. H., Nash, V. L., and Granger, H. R.: The Vasopressor Activity of Some New Orally Active Sympathomimetic Amines.** J. Pharmacol. & Exper. Therap. **92:** 207 (March), 1948.

The vasopressor effects of a small group of orally active phenyl and cyclohexylisopropyl amines were investigated.

These compounds produced prolonged vasopressor effects comparable to amphetamine in unanesthetized and anesthetized dogs. The central nervous system stimulating effect could be diminished by saturation of the ring of several phenyl compounds to produce cyclohexyl compounds.

GODFREY.

**Burch, G., and Ray, T.: Cardiovascular System as the Effector Organ in Psychosomatic Phenomena.** J.A.M.A. **136:**1011 (April 17), 1948.

Burch and Ray emphasize the extreme susceptibility of the cardiovascular system to psychic influences in both health and disease and cite literature illustrating the well-recognized central (cardiac) and peripheral (vascular) manifestations which result from emotional stimuli. The cardiac effects embrace increase in cardiac output, electrocardiographic changes, various arrhythmias, the precipitation of angina, and even sudden death. The peripheral effects consist of vasodilation and vasoconstriction with resultant changes in systemic blood pressure and in local temperature and color.

The authors point out that heretofore, the approach to the study of the cardiovascular reactions to emotional stimuli has rested largely upon clinical evaluation and observation, blood pressure determinations, electrocardiographic and thermometric studies, and measurements of cardiac output. Because of the accessibility and reactivity of the blood vessels of the digits, the authors feel that quantitative plethysmographic studies of these vessels afford another objective approach to the problem.

By means of a portable plethysmographic apparatus they recorded the changes of vascular volume of the tips of the index finger and/or second toe in a series of normal subjects and patients with known psychiatric difficulties, usually anxiety neurosis. Test stimuli of various types resulted in immediate and definite plethysmographic changes (reduction in the volume of pulse deflections, reduction in the total volume of the part, and alterations in the alpha deflections). The authors offer this objective method of study as another clinical means of exploring the psychosomatic cardiovascular reactions.

HANNO.

**Smith, H. W.: Hypertension and Urologic Disease.** Am. J. Med. **4:**724 (May), 1948.

The author points out that it is not yet proved that human hypertension has its origin in either pathologic or functional disturbances of the renal circulation, despite all of the knowledge available from the Goldblatt experiment. An equally good interpretation of the data available is in terms of a generalized pathologic process which, by arteriolosclerosis and possibly other

mechanisms, attacks the renal parenchyma along with other organs. Sympathectomy lowers the blood pressure in some instances, but it has not yet been demonstrated that it changes the temporal progress of the disease.

The fallacies involved in dependence either on the blood pressure or the patient's symptoms as a guide in evaluating progress of the disease and the value of various therapeutic procedures is pointed out. Statistical data on blood pressure among the general population indicate that the incidence of essential hypertension is quite low before the age of 20 years, affects 25 per cent of the general population who have reached the age of forty years, and is present in 60 per cent of elderly persons.

The available evidence points to the fact that the incidence of hypertension is not increased by urologic disease and that the incidence of urologic disease is no greater among hypertensive than among normotensive subjects. Review of the literature on unilateral nephrectomy has revealed a cure of the hypertension in only forty-seven instances of 242 reported operations. The author concludes that the advisability of nephrectomy must rest upon conservative and recognized surgical indications and not upon the hope of reducing blood pressure.

WOODS.

**Ostling, G.: The Significance of the Speed of Injection for the Therapeutic Effect of K-Strophanthin.** Acta med. Scandinav. **129:**77 (No. I), 1947.

Because of contradictory assertions in the literature regarding the advisability of slow as opposed to rapid injection of strophanthin, the author assessed the effect of daily one- to two-hour infusions of 0.5 mg. or less on twenty-three patients who had congestive failure with or without auricular fibrillation. Seventeen improved, with increased diuresis, loss of weight, and lowered heart rate. One died fourteen hours after a stenocardial attack which followed the infusion by an hour. The results were thought comparable to those obtained with faster injection, and there appeared to be no advantage in extending the time of injection beyond one minute. The author believes that the significance of the speed of injection of strophanthin has been overstressed.

SAYEN.

**Mainzer, F.: Electrocardiographic Study of Typhoid Myocarditis.** Brit. Heart J. **9:**145 (Oct.), 1947.

The electrocardiographic findings in 254 tracings from 106 patients are reported. A few had paratyphoid infections. Thirty-nine had one tracing during convalescence; sixty had from three to seven tracings during and after the febrile state; seven were treated with chinine-bismuth-iodide and had one tracing during convalescence. Sixty of the 106 patients had abnormal tracings. The changes consisted of flattened, absent, or negative T waves, depressed or elevated S-T segments, low voltage with slurring or notching of the ventricular complexes, axis deviation to the right or left, and occasionally the appearance of Q waves. These changes occurred both with tachycardia and with bradycardia. A prolonged P-R interval was seen only once. The changes were twice as common in the febrile state as in convalescence. The changes persisted for from one to three weeks. Exertional tachycardia was present for weeks. It was uncertain whether the changes in the patients treated with chinine-bismuth-iodide were due to the disease or to the treatment.

The abnormal tracing is regarded as an expression of typhoid myocarditis. Clinically, typhoid myocarditis is manifested commonly by "forward failure" and in severe cases, by both "forward" and "backward" failure.

SOLOFF.

**Segers, M., Vastesaeger, M., and Denolin, H.: Intraventricular Conduction Defects.** Acta Cardiol. **2:**166, 1947.

The classical electrocardiographic pattern of bundle branch block may be augmented by at least three additional types of intraventricular conduction disturbances:

1. Incomplete bundle branch block. This type is demonstrated in one example with incomplete left bundle branch block where late activation of the left ventricular surface and slurring

in the vectorcardiogram was present without reversal in rotation of the vector which is commonly noted in true bundle branch block. The slurring of the QRS complexes in standard limb leads in such instances is usually confined to the rising portion of QRS.

2. Focal intraventricular block. In this type, slurring of QRS is confined to the descending limb of QRS and is seen in the final portion of the ventricular loop of the vectorcardiogram. The pattern may represent lesions of the terminal branches of the conduction system.

3. Complex (bilateral) intraventricular block. In classical bundle branch block spontaneous changes in the form of the QRS complexes may occur and these may signal additional regions of impaired conduction. This is demonstrated in an example of left bundle branch block where the configuration of the standard limb leads changed spontaneously. Left bundle branch block was always present but special right-side chest leads revealed that during the period of change an additional conduction delay appeared over regions of the right ventricle. It confirmed the assumption that left bundle branch block was present with a focal lesion over the right ventricle.

HECHT.

**Morelli, A., and Salvi, P.: Treatment of Essential Hypertension With Vitamin K.** Progr. Med. (Naples) **3**:611, 1947.

The authors studied the action of synthetic vitamin K as a possible hypotensive drug. In ten cases of essential hypertension, intravenous vitamin K was given in dose of 10 mg., and blood pressure variations and serum cholinesterase were studied. A transitory drop in blood pressure was observed which reached a maximum value within thirty minutes; this was followed by a gradual rise to the previous level. A parallel drop in the value of the serum cholinesterase was observed.

The mechanism of action of the drug is believed to be an increase in the parasympathetic tonus resulting from a decreased destruction of acetylcholine by the cholesterase.

LUISADA.

**Vincent, D.: The Effect of Certain Cardiac Glucosides on Serum Cholinesterase.** Compt. rend. Soc. de biol. **141**:843 (Aug.), 1947.

Danielopolu's assumption that the action of digitalis compounds may be explained as primary inhibition of cholinesterase was tested in vitro by titrating horse serum containing various amounts of digitoxin, lanatoside C, ouabain, and scillaren against a solution of acetylcholine. No appreciable cholinesterase inhibition was observed. The cholinesterase activity of the serum of guinea pigs injected with digitoxin, ouabain, or lanatoside C (2 mg. per kilogram) was not appreciably altered when the samples were obtained prior to death from digitalis intoxication.

HECHT.

**Bregante, L. J.: The Augmentation of the Effects of Vagal Stimulation Upon the Auricular Muscle of the Turtle by Veratrine and Sulfocyanate.** Compt. rend. Soc. de biol. **141**:846 (Aug.), 1947.

The negative chronotropic effect of vagal excitation (faradic stimulation) is augmented by veratrine sulfate in concentration of 1:100,000 to 1:200,000 and by sodium sulfocyanate in concentration of 1:10,000 to 1:20,000. It is assumed that the two substances lower the cardiac threshold to the inhibitory effects of potassium ions which may play a part in the cardiac response to vagal stimulation.

HECHT.

**Migliaro, E.: Hypersensitivity of Cardiac Muscle to Potassium Ion Following the Administration of Veratrine and Sulfocyanate After Complete Atropinization.** Compt. rend. Soc. de biol. **141**:847 (Aug.), 1947.

Isolated heart preparations of frog and turtle suspended in Ringer's solution containing large amount of potassium revealed a striking sensitivity to the inotrophic action of potassium following the administration of veratrine and sulfocyanates even after atropine had been added in sufficient quantities to the perfusion fluid. The decrease in amplitude of myocardial contraction when the

preparation is in Ringer's solution containing three times the amount of potassium ranges from 20 to 50 per cent. Following administration of the two compounds the decrease amounts to 75 to 100 per cent of the normal amplitude. HECHT.

**Binet, L., and Burstein, M.: The Reaction of the Peripheral Vascular System of the Dog to Stimulation of the Central End of the Vagus Nerve.** Compt. rend. Soc. de biol. **141**:971 (Oct.), 1947.

Faradic stimulation of the central end of a completely vagotomized animal results in marked rise in arterial blood pressure. When the circulation of the paw of these animals is measured by canulation and perfusion with homologous blood it can be demonstrated that weak faradic stimulation results in increased flow through the extremity while strong stimulation results in a sharp decrease. It is argued that strong faradic stimulation enhances the secretion of humoral substances, presumably epinephrine, and that such endocrine factors contribute to the response obtained. It is stated that in cross circulation experiments blood obtained during strong faradic stimulation is capable of producing vasoconstriction when perfused throughout the extremity of a nonstimulated animal. HECHT.

**Padilla, T., Cossio, P., Berreta, J. A., and Alvarez, G. H.: Sympathectomy in Essential Hypertension.** Medicina **7**:429 (Oct.), 1947.

Twenty-nine patients were subjected to postganglionic and bilateral supra- and infradiaphragmatic splanchnic resection (Smithwick), and five, to an infradiaphragmatic resection alone (Adson). Eleven of these patients presented evidence of severe retinal involvement (Grade III and IV), but none had appreciable renal impairment. The early results were encouraging, but after a period of two years, less than 20 per cent were benefited by the operation. The procedure is not recommended as a treatment for the hypertensive syndrome, even in selected cases. The operative mortality was 10 per cent. HECHT.

**Chardon, G., Gross, A., and Fourrier, A.: On the Cause of Cardiac Acceleration During Anoxia.** Compt. rend. Soc. de biol. **141**:1050 (Oct.), 1947.

The increase in heart rate following inhalation of a mixture containing 10 per cent oxygen appears to be the result of stimulation of the carotid sinus. In the denervated animal, no alteration in heart rate is observed. It is suggested that during induced hypoxia epinephrine is excessively secreted. In addition to the possible effects of low oxygen tension on the central nervous system as the cause for tachycardia, a temporary hyperadrenalinemia is implicated.

HECHT.

**Charlier, R., and Philippot, E.: Heart and Carotid Sinus. II. Endo-sinusal Hypotension and Right Ventricular Pressure. III. Endo-sinusal Hypotension and Cardiac Dynamics in the Sympathectomized and in the Completely Denervated Heart of Dogs.** Arch. internat. de pharmacodyn. et de thérap. **75**:135 (Nov.), 1947.

In nine anesthetized dogs occlusion of the carotid sinus resulted in a prompt increase in right ventricular pressure obtained by cardiac catheterization. The cardiac output increased from 20 to 70 per cent. During the experiment an increase in oxygen consumption and in pulmonary ventilation occurred and the arteriovenous oxygen difference decreased. As the arterial pressure rose considerably, cardiac work increased from 50 to 120 per cent. Intra-auricular pressures, however, remained relatively unchanged. A sharp fall in right ventricular pressure and in cardiac output, independent of changes in arterial pressure, was noted in two instances following section of the vagus nerve. The response of the cardiovascular system to occlusion of the carotid sinus, and particularly the rise in cardiac output, decrease in arteriovenous oxygen difference with high oxygen values for the mixed venous blood, and the rise in arterial pressure, occurred even when sympathetic and parasympathetic fibers to the heart were sectioned. The pressure response following occlusion of the sinus must, in part, be explained by a reflexly increased cardiac output.

HECHT.

**Fauteux, M.: Cardiac Resuscitation.** J. Thoracic Surg. **16**:623 (Dec.), 1947.

The author defines cardiac resuscitation as "full and durable restoration, in due time to avoid eventual death, of the essential functions of a heart which has lost its power to propel blood, and which, in all appearance, is unable to recover its effective value as a pump." He then points out that restoration in the strict sense is rare, clinically and experimentally, following cardiac standstill and ventricular fibrillation.

As a result of an extensive experience with experimental studies of resuscitation of the heart from cardiac standstill and ventricular fibrillation, the author believes that the following drugs, employed properly, are of value: (1) Procaine, 1.0 or 2.0 c.c. of a 2 per cent solution, injected slowly into the right or left auricle, has a significant effect on the irritability of the heart, decreasing it greatly. Injection of the procaine into the blood stream is more effective than topical application to the epicardium. (2) Barium chloride, 1.0 to 2.0 c.c. of a 0.5 per cent solution, is effective in increasing the force of the heart beat, and also in increasing cardiac tone. Overdosage causes death in systole. The drug can be administered also by injection directly into the auricle. (3) Epinephrine, 0.5 to 1.0 c.c. of a 1:1,000 solution (0.1 per cent), is of value in increasing the rate and strength of the heart, but in some instances can initiate ventricular fibrillation.

Certain physical factors are also useful in cardiac resuscitation: (1) Cooling of the overheated heart resulting from repeated electrical shocks is of value. (2) Cardiac massage is immensely important in restoring coordinated beats to the heart which is in standstill. (3) Electrical shocks are of value in defibrillating the heart which is in ventricular fibrillation. (4) Intracardiac transfusion may aid in overcoming peripheral circulatory failure.

Fauteux points out that the essential accidents which must be prevented during an elective operation on the heart are: (1) hemorrhage, (2) serious circulatory disturbances due to unwise manipulations, (4) reflexes of various nature, (5) cardiac standstill, and (5) ventricular fibrillation. All of these accidents can be managed by present-day knowledge but are dependent on the surgeon's experience with animal experiments, on an adequate armamentarium in the operating room, and finally, on the electrocardiogram as a constant recorder of the effects of manipulation on the rhythm of the heart. LCRD.

**Harken, D. E.: The Removal of Foreign Bodies From the Pericardium and Heart: A Moving Picture Demonstration.** J. Thoracic Surg. **16**:701 (Dec.), 1947.

The author employed motion pictures to demonstrate three operations illustrating important points in the removal of foreign bodies from the heart and the pericardium. There were 134 missiles removed from the mediastinum in his experience in England. Fifty-five were pericardial and thirteen were in the chambers of the heart. Seventeen cardiotomies were performed and there were no deaths.

It was felt that the following four indications should determine whether foreign bodies should be removed from the heart: (1) to prevent embolus of the foreign body or associated thrombus; (2) to reduce the danger of bacterial endocarditis; (3) to avoid recurrent pericardial effusions; and (4) to reduce damage to the myocardium. It should be added, however, that in their experience, the number of foreign bodies which were not operated upon was greater than those which were removed. The ones not operated upon produced, of course, no symptoms.

The operation demonstrated in the first motion picture revealed an abscess in the pericardial sac in which 18 c.c. of purulent material was present around the foreign body. On culture the organism grown was *Clostridium welchii*. Dislocation of the heart during the maneuver produced significant changes in the electrocardiogram which was being made at the time of the operation. These changes included right bundle branch block. At the completion of the manipulation of the heart, normal rhythm was restored. The patient made an uneventful recovery. The author feels that bathing the heart with Novocain (1 per cent) is important in preventing abnormalities of rhythm; the drug also has a potentially specific depressor action on the heart.

The second motion picture showed an operation for the removal of a missile from the right ventricle. There was a zone of damage to the overlying myocardium. By means of two staggered rows of hemostatic U sutures of number zero chromic catgut, hemostasis was maintained while the heart muscle was incised and the foreign body removed by the grasping forceps. Four trans-

fusions of 1,000 c.c. of fresh whole blood were used to replace the estimated loss of 800 c.c. of blood during this manipulation. The patient withstood the procedure well and hemostasis was adequate after the sutures were tied and a free patch graft of pericardium was tacked over the incision into the myocardium. It was also felt important to leave a decompression window several centimeters in diameter in the pericardium so that fluid could escape into the left pleural space. The chest wall was carefully reconstructed without drainage. This patient also made an uneventful recovery.

The third operation showed a patient who had been operated upon twice before in an attempt to remove a foreign body which lay in the right ventricle. The illustrated operation demonstrated that the removal was accomplished successfully and it also demonstrated that the previous cardiotomy site had healed satisfactorily. LORD.

**Biorck, G., Gohle, O., and Westman, C.: Partial A-V Block and Duodenal Ulcer.** Acta med. Scandinav. **130:167** (No. 2), 1948.

Two male subjects, 14 and 26 years of age, both with duodenal ulcer and disturbed auriculoventricular conduction, are reported upon. One had orthostatic tachycardia which could be abolished by ergotamine, which, however, threw the patient from heart block of minor grade into a 2:1 or 3:1 block. Atropine would shorten the P-R interval. The older patient's auriculoventricular conduction time was 0.27 to 0.28 second in recumbency and became normal on standing.

The authors discuss the possibility of both ulcers and auriculoventricular conduction disturbances having a common mechanism consisting of increased vagal tone or some disturbance of the parasympathetic cerebral centers. A cardiologic survey is recommended for children and young adults who develop peptic ulcer as an aid in deciding whether the cause is local or whether the ulcer is one manifestation of a systemic disease. SAYEN.

**Elmquist, A., and Rydin, H.: The Influence of Muscular Exercise on the Tolerance of Digitalis in Guinea-Pigs.** Acta physiol. Scandinav. **15:63** (No. 1), 1948.

Investigating the proposition that cardiac patients require more digitalis with increased physical exertion, the authors administered Digitotal subcutaneously for one month to two groups of guinea pigs. One group was forced to exercise for periods up to one hour after each injection. A third group served as controls. At the end of the experiment the minimal lethal dose of Digitotal was determined for all survivors by an intravenous injection.

The exercised guinea pigs were able to tolerate more digitalis than those not exercised, and the minimal lethal dose of the latter was smaller. The exercised guinea pigs required a minimal lethal dose comparable to that of the controls. These differences were analyzed statistically and proved significant. Muscular exercise is thus thought to increase the guinea pig's tolerance to digitalis; continuance of the investigation on clinical material is suggested. SAYEN.

**Broden, B., Hanson, H. E., and Karnell, J.: Thoracic Aortography, Preliminary Report.** Acta radiol. **29:181** (No. 2), 1948.

The results of studying three patients by Diodrast aortography after a technique devised by Radner (Acta Radiol. **29:178**, 1948) are reported. A cardiac catheter (No. 7 to 9) was passed up the radial artery after this vessel had been exposed in the upper third of the forearm and a small transverse incision made in it between two clamps. The catheter could then be passed into the ascending aorta, the right radial artery directing it more satisfactorily than the left. The abdominal aorta and the opposite arm were compressed in order to delay transport of the 70 per cent Diodrast solution from the thoracic aorta. Fifty c.c. were injected as rapidly as possible. The resistance was very high and an average of seven seconds was required for each injection. Local anesthesia and light sedation were used. X-ray films were made simultaneously in two planes at a rate of one film per second. The aorta was well visualized in all three patients. Two of this number showed a coarctation. The radial artery was sutured satisfactorily in two of the patients and ligated without incident in the other. One patient developed considerable vasospasm during passage of the catheter.

The authors recommend their modification of Radner's method for the study of all aortic lesions but especially coarctation and atypical patent ductus arteriosus. They are attempting to devise a mechanical device to achieve a more rapid injection. SAYEN.

**Fabricius, B.: Kymographic Studies of the Function of the Auricle.** Acta radiol. **29**:152, 1948.

Previous views as to the type of contraction of the auricular appendage are discussed and a study reported of the relation of left auricular appendage waves to the movements of the right atrial and the left ventricular border based on thirty-eight combined roentgen-kymographic and electrocardiographic recordings in twenty-two subjects. The movement of the auricular appendage was quite variable, no regular correlation with the motion of the rest of the heart being obtained. The author agrees with the observations on mammalian hearts made by Rollhäuser (Morphol. Jahrbuch **88**:249, 1943) that the auricular appendage has no propulsive function but serves as a complementary space during ventricular systole to keep the surface of the heart constant, thus serving as an elastic filling material for the deep niches at the base in systole. When aneurysm of the pulmonic artery or of the ascending aorta fills the niches the auricular appendages have been found greatly decreased in size. SAYEN.

**Clerc, A., and Quincaud, A.: Identical Electrocardiograms With Cardiac Apex Formed by Right or Left Ventricular Myocardium.** Compt. rend. Soc. de biol. **142**:151, (Feb.), 1948.

After ligatures were applied to both venae cavae and the azygos vein, the beating dog's heart was sectioned so that it was divided in two parts; one, the base of the heart with the great vessels attached, the other the apex of the left ventricle and the anterior aspect of the right ventricle. Lead II was recorded with the fragments in their normal relation, and then with apical fragment arranged so that the right ventricular myocardium formed the apex. Lead II appeared the same under both conditions. This led the authors to conclude that the form of the electrocardiogram is determined by the position of the heart and that it is the heart as a whole which determines the electrical axis. SEGALL.

**Franck, C., Grandpierre, R., and Royer, P.: Transitory Apnoea in Man Induced by Breathing a Mixture Rich in Oxygen During a State of Anoxaemia.** Compt. rend. Soc. de biol. **142**:376 (March), 1948.

Human subjects were first rendered anoxemic by breathing pure nitrogen during one to four minutes; the gas was then changed to ordinary air or pure oxygen. This sudden change resulted in transitory apnea which tended to be longer the richer the oxygen content of this mixture. On the other hand, restoration of normal breathing is more regular and progressive with the richer than with the poorer oxygen mixtures. SEGALL.

**Charlier, R.: The Role of the Carotid Sinus and the Cardio-Aortic Region in Reflex Regulation of Cardiac Output.** Acta Cardiol. **3**:1 (Jan.), 1948.

This paper presents in greater detail the findings reported in another communication (Arch. internat. pharmacodyn. et de thérap. **75**:135, 1947). Clamping off both common carotid arteries results in a striking increase in cardiac output induced by an increase in venous inflow. This may come about by venous constriction and/or by the opening of possible arteriovenous channels (decrease in arteriovenous oxygen difference) or by both. It is assumed that the greater part of the increase in arterial blood pressure following the clamping of the carotid arteries or section of the four depressor nerves is the result of alteration in stroke volume. The conclusions are at variance with those reported by Heymans and his collaborators. HECHT.

**Lequine, J., Denolin, H., and Verniory, A.: Dextrocardia and Septal Defects.** Acta Cardiol. **3**:56 (Jan.), 1948.

Two examples of dextrocardia both complicated by intraventricular septal defects are presented. The first resembled a tetralogy of Fallot, the second an Eisenmenger complex. From the

oxygen consumption and from arterial and (peripheral) venous oxygen content, the cardiac output, pulmonary circulation, and flow of blood through abnormal shunts were determined according to formulas by Van Slyke and by Bing. In the first case the venoarterial shunt was estimated as 15 per cent (0.38 liter), in the second as 50 per cent of the cardiac output (1.21 liters).

HECHT.

**Cooper, F. W., Jr., Harris, M. H., and Kahn, J. W.: Ligation and Division of the Abdominal Aorta for Metallic Embolus From the Heart.** Ann. Surg. **127**:1 (Jan.), 1948.

The authors present a case report in which excision of the bifurcation of the aorta was necessitated by erosion of a portion of the vessel by a foreign body within its lumen. The patient had sustained a penetrating gunshot wound of the left arm and chest, and subsequently x-ray examination revealed a 45 caliber bullet at the bifurcation of the aorta. The missile was removed surgically from the vessel, and the aorta was ligated below the origin of the inferior mesenteric artery. An uneventful recovery occurred with a gradual increase in the circulation of the lower extremities.

It was the opinion of the authors that the good therapeutic result was due to the fact that the occlusion of the aorta, initiated by the foreign body, occurred over a period of several weeks, and that consequently an adequate collateral circulation had developed in the interval. Since the skin temperature of the toes actually increased after operation, it was felt that the procedure had removed a source of irritation of the arterial wall and hence eliminated the reflex vasoconstriction which results from such a condition.

ABRAMSON.

**Segre, G.: On the Mechanism of Digitalis Action.** Arch. internat. de pharmacodyn. et de thérap. **75**:227 (Jan.), 1948.

The glucose metabolism of intact and hemolyzed horse erythrocytes is influenced by digitalis and by strophanthin in pharmacologically active concentrations. A decrease in glucose uptake is noted together with an increase in oxidation of lactic acid. The action is unimpaired and oxidation to lactic acid occurs in the presence of carbon monoxide and of cyanide. It is argued that the digitalis bodies act like a coenzyme and that they participate in glucose metabolism in the absence of coenzymase. It is assumed that these compounds may act as hydrogen carriers in an oxidation-reduction system.

HECHT.

**Farah, A., and Maresh, G.: Determination of the Therapeutic Irregularity and Lethal Doses of Cardiac Glycosides in the Heart-Lung Preparation of the Dog.** J. Pharmacol. & Exper. Therap. **92**:32 (Jan.), 1948.

The authors found that on a molar basis the cardiac glycosides have the following order of decreasing potency: g-strophanthin, digoxin, digitoxin, oleandrin, and lanatoside B. The average ratios of irregularity dose to therapeutic dose, and lethal to therapeutic dose were the same for all five glycosides studied. These findings differ from other reports in which other methods and preparations were used.

GODFREY.

**Gruber, C. M., and Keyser, G. F.: The Effects of Analgesic Drugs Upon Excised Frog and Terrapin Cardiac Vagus Nerve.** J. Pharmacol. & Exper. Therap. **92**:59 (Jan.), 1948.

Racemates A and B of 1-amino-1-phthalidylpropane hydrochloride, aminopyrine, antipyrine, and acetanilid were studied. The cardiac rate and contraction were measured. Racemates A and B when applied to the perfused frog heart decreased cardiac contraction and rate. The results with aminopyrine and antipyrine were variable. All drugs studied decreased the response of the heart to stimulation of the cardiac vagus nerve (terrapin). Racemate A was found to be twice as toxic to the heart as Racemate B.

GODFREY.

**Farah, A., and Maresh, G.: The Influence of Sulfhydryl Compounds on Diuresis and Renal and Cardiac Circulatory Changes Caused by Mersalyl.** J. Pharmacol. & Exper. Therap. **92**:73 (Jan.), 1948.

In a well-controlled series of experiments in which both anesthetized and unanesthetized animals of two species (rabbit and dog) were used, the authors demonstrated that the diuresis

caused by mersalyl was abruptly and completely inhibited by 2, 3-dimercaptopropanol (BAL). The diuresis caused by intravenous infusion with sodium chloride and aminophylline was not inhibited by BAL. Cysteine hydrochloride and glutathione had no effect upon the diuresis of mersalyl even when given in very large doses. BAL, cysteine hydrochloride, and glutathione have all been found to be effective in inhibiting the cardiotoxic effects of mercurials.

To correlate the cardiotoxic inhibiting effects with the renal effects of BAL, cysteine hydrochloride, and glutathione, animals were given infusions of mersalyl and simultaneous records were made of blood pressure, electrocardiogram, and urinary output. When cardiotoxic manifestations occurred the sulfhydryl compound was given intravenously. BAL was found to inhibit both the cardiotoxic effects and the diuretic effect of the mercurial. Cysteine hydrochloride and glutathione inhibited only the cardiotoxic action.

The characteristic diuresis caused by mersalyl is initiated by a transient reduction in urinary output. This was shown to be due to a reduction in kidney blood flow. This reduction in blood flow is completely abolished by all three of the sulfhydryl compounds (BAL, cysteine hydrochloride, and glutathione). Since only BAL inhibits the diuresis, the evidence suggests that mercurials affect more than one process in the renal excretatory process. GODFREY.

**Leriche, R., and Morel, A.: The Syndrome of Thrombotic Obliteration of the Aortic Bifurcation.** Ann. Surg. **127**:193 (Feb.), 1948.

The authors describe a syndrome related to a slow thrombotic obliteration of the terminal portion of the abdominal aorta. Patients with this condition are generally young men, who complain of an inability to maintain an erection and, eventually, permanent sexual impotency, extreme fatigue of both lower extremities, atrophy of these limbs, pallor of the legs and feet, even when standing, but no trophic changes either of the skin or of the nails. Examination reveals an absence of all pulses in the lower extremities and no oscillometric readings, even at the thigh, with a slight thrill present near Poupart's ligament. Pulsations can be felt in the aorta only above the level of the umbilicus. Although aortography will help to support the diagnosis, it should not be used in the presence of a reduced cardiac output or when the legs show cyanosis, since in such instances it may lead to the extension of the thrombosis with a fatal outcome. The fatigue in the legs is not the typical intermittent claudication but an extreme weariness which appears soon after the onset of walking and sometimes during standing. The pallor of the skin is quite striking, and this becomes even more marked when the limbs are elevated.

The pathologic change observed either at operation or post-mortem examination consists of a thrombotic process, generally beginning in one of the common iliac arteries and extending upward into the aorta. This hampers the blood flow to the opposite side but does not stop it entirely for some time. Ultimately the result is the obliteration of both iliac arteries and the aortic bifurcation. Less frequently the process first begins in the aorta and secondarily extends down into the iliac arteries. Generally there is an intensive periarteritis which attaches the thrombotic segment of the aorta to the surrounding tissues.

Aortic thrombosis may last for as long as five to ten years but eventually gangrene occurs. This is not sudden and is not always bilateral. It is preceded by an increasing muscular atrophy of the legs and thighs and an increasing impairment in walking. The acute terminal stage is ushered in by the appearance of edema and the development of a general violacious hue to the legs, with ecchymosis followed by ulcers on all pressure points; finally gangrene occurs. The lesions progress slowly. The prolonged survival can be explained by the extensive collateral anastomosis that is formed as the main channels slowly become thrombosed. The onset of the terminal period is probably due to upward and downward extension of the thrombosis.

According to the authors, the only treatment which has produced satisfactory results is resection of the thrombosed portion of the aorta and the obliterated iliac arteries, together with bilateral upper lumbar ganglionectomy. It is their belief that by removal of the thrombosed segments a source of vasoconstrictor reflexes is eliminated and, furthermore, the spreading thrombosis is checked. ABRAMSON.

**Kaldeck, R.: Transient Hemiplegia Following Electroconvulsive Treatment.** Arch. Neurol. & Psychiat. **59**:229 (Feb.), 1948.

The author presents a case of transient hemiplegia of several days' duration which developed following electroconvulsive treatment in a physically normal young woman with a schizoaffective psychosis. Electroshock treatment was given at weekly intervals. Two days after her tenth electroshock treatment she was unable to get up from bed. Neurological examination two days later showed that she was conscious and in fairly good contact, but tense and at times unwilling to cooperate. Her left arm and hand were limp and totally paralyzed; her left leg was weak and partially paralyzed. There were definite Hoffmann and Oppenheim signs on the left; the Babinski sign was equivocal. Two days later she showed pronounced improvement in the motor power of the left leg but was still unable to move the arm; slight movements of the hand were possible. On each of the following days the condition continued to improve. A year after the incident a neurological examination revealed nothing abnormal. A few weeks after termination of the shock treatment she relapsed into her previous mental condition. The experience of her hemiplegia has now been included in her paranoid ideation, and she refuses to submit to further electric treatment. Finally an electroencephalogram was obtained which proved to be normal.

The transient hemiplegia in this case is explained by the author on the basis of a vascular spasm. The arteriolar constriction must have lasted long enough to cause structural damage.

BELLET.

**Gruhzit, O. M., Fisken, R. A., and Cooper, B. J.: Tetraethylammonium Chloride. Acute and Chronic Toxicity in Experimental Animals.** J. Pharmacol. & Exper. Therap. **92**:103 (Feb.), 1948.

Tetra-ethyl-ammonium chloride was administered both orally and parenterally to albino mice, albino rats, and dogs. With large doses, no matter what the route of administration, the animals died of respiratory failure within ten to thirty minutes. The following signs occurred before death: "Severe incoordination, flaccid prostration, respiratory and cardiac depression, marked ptosis and edema of eyelids, mydriasis, ocular muscle paralysis (inversion of eyeballs), erythema of ocular, nasal, and less so of buccal membranes, paralysis of accessory respiratory muscles of chest, and death from respiratory and circulatory collapse." Sublethal doses were well tolerated when given over long periods of time, even when the amount of drug given was large enough to cause some of these signs for two to three hours after administration. During chronic toxicity experiments with sublethal doses there were no hematologic, renal, or hepatic signs of damage that could be detected by blood counts, total blood nonprotein nitrogen, albumin-globulin fractions, bromsulfalein blood concentration, and urin analysis.

Necropsy lesions in acute toxicity experiments consisted in "severe congestive blood stasis and petechial hemorrhages in visceral organs, liver, lungs, kidneys, spleen, gastrointestinal tract, urinary bladder, and brain." Edema and necrotic changes were noted around the central veins of the liver. Cloudy swelling was noted in the kidneys along with changes in the cytoplasm of the cells lining the loop of Henle.

Repeated administration of sublethal doses produce no significant pathologic lesions.

GODFREY.

**Lipschitz, W. L., and Stokey, E.: Diuretic Action of Formoguanamine in Normal Persons.** J. Pharmacol. & Exper. Therap. **92**:131 (Feb.), 1948.

The authors have previously reported the mode of diuretic action of formoguanamine (J. Pharmacol. & Exper. Therap. **83**:235, 1945). Formoguanamine has been found to be markedly more effective as a diuretic than urea. Toxicity studies on dogs and rabbits failed to reveal any significant toxicity.

Formoguanamine was administered to eight healthy male volunteers in doses from 3.5 to 11.0 mg. per kilogram of body weight. Its diuretic action was compared with that of caffeine and theobromine. It was found to give a more consistant diuresis than either caffeine or theobromine. Both sodium chloride and water excretion were increased. No toxicity was noted in the eight volunteers.

GODFREY.

**McNamara, B., Krop, S., and McKay, E. A.: The Effect of Calcium on the Cardiovascular Stimulation Produced by Acetylcholine.** J. Pharmacol. & Exper. Therap. **92**:153 (Feb.), 1948.

Acetylcholine causes a pressor response in animals that have been atropinized. This response, in turn, may be blocked by nicotine. The pressor response caused by acetylcholine is believed to be due to ganglionic stimulation and its blockage by nicotine to be due to ganglionic blockage.

The authors showed that by administering calcium they were able to inhibit the ganglionic blocking action of nicotine so that the acetylcholine effect was not abolished. This could be demonstrated in both the intact animal and the isolated heart. They also demonstrated that calcium potentiates the epinephrine effect upon the heart. They believe that aceltycholine acts directly upon the cardiac musculature by means of liberating an epinephrine-like substance. The fact that calcium potentiates epinephrine effects and also overcomes nicotine blockage sheds further light on its cardiac effects and the mechanism by which it acts upon the heart.

GODFREY.

**Gore, I.: Myocardial Changes in Fatal Diphtheria. A Summary of Observations in 221 Cases.** Am. J. M. Sc. **215**:257 (March), 1948.

The author warns of certain ominous potentialities in connection with the incidence of diphtheria. Though there is a continuing downward trend in the United States since the practice of immunization became widespread, the disease has not been conquered, and the tremendously decreased carrier rate has been associated with a rising susceptibility, as indicated by the Schick test. Furthermore, the reduced exposure to diphtheria bacilli with the concurrent loss of its stimulating effect has contributed to the more rapid waning of artificially induced immunity. Such circumstances set the stage for a widespread reappearance of the disease should virulent organisms be introduced into the population. The present incidence of diphtheria in several of the European countries makes this possibility far from remote. It was, therefore, considered appropriate to report a study of that sequel of diphtheria which is most often lethal: myocarditis.

The study is based on a review of the autopsy records and slides of 221 fatal cases of diphtheria accumulated at the Army Institute of Pathology. Material from the heart was available for review in 205 of these. Myocarditis occurred in 143 (70 per cent). It was found that the longer the survival after the onset of diphtheria, the greater the incidence of this complication. Neuritis had a similar relationship to survival time, but it appeared still later and was less frequent. These two sequellae were not related causally to each other, and neither age nor color appeared to have any influence upon them.

Pathologically, the hearts were dilated, with flabby, pale, or mottled musculature, and frequently they were enlarged. Microscopically, there was a primary toxic degeneration of the fibers. The inflammatory response, which culminates in scarring, appeared to be secondary to the muscle injury.

In one-third of the cases the manifestations of myocarditis appeared at a time when the patient seemed to be well on his way to convalescence. The interval between diphtheria and the onset of cardiac symptoms has been designated the deceptive interval of apparent improvement. The importance of administration of antitoxin early and in adequate quantities is re-emphasized as a measure to prevent myocarditis (and neuritis). The designation of myocarditis as a sequel of the pharmacologic effect of the toxin rather than as an unexpected complication may contribute to the early and more frequent recognition of myocarditis.

A shock-like state following diphtheria must be recognized as a frequent manifestation of myocardial weakness lest the vigorous administration of intravenous fluids to combat it result in a fatal termination.

DURANT.

**Slevin, J. G.: New Test in Diagnosis and Surgical Treatment of Varicose Veins.** Am. J. Surg. **75**:469 (March), 1948.

The author points out that there is considerable difference of opinion concerning the importance of incompetent communicating veins in the production of superficial varicose veins. Some workers believe that this type of vessel is rare and unimportant and that the reflux occurs

through the lesser saphenous vein. On the other hand, others, including the author, are of the opinion that incompetent communicating veins are the primary cause of recurrence after injection of a sclerosing solution, since backflow through the incompetent perforator either prevents a firm sclerosis or causes recanalization.

In order to determine the exact site of "blowouts," the author utilized the multiple tourniquet test. This is performed with the patient lying on the examining table with the lower extremity elevated until the superficial veins are empty. Tourniquets are then applied to the upper, middle, and lower thigh, and at least one is applied below the knee. When the patient stands, the tourniquets are removed from below upward within three to five seconds. A rapid filling of any segment before the highest tourniquet is removed indicates a Trendelenberg double positive reaction. The segment is noted and the test repeated so as to determine the exact location of the "blowout."

In the treatment of varicose veins, the author found sodium morrhuate to be the best sclerosing agent. Up to 4.0 c.c. of this solution is a safe amount to inject at one time if spread over two or more segments of the vein. By application of an elastic bandage to the leg for the first twenty-four hours after injection, less solution is needed and disfiguring knots in the leg are avoided. The author obtained effective cures in 96.6 per cent of his cases using high and low ligation technique, which permits the patient to return to work in two or three days. Vein stripping, as advocated by other workers, was found to be an unnecessary procedure in all but the exceptional case. ABRAMSON.

**Cooper, W. M.: Treatment of Varicose Ulcer.** Am. J. Surg. 75:475 (March), 1948.

The author precedes his discussion of the treatment of varicose ulcer with a section on the pathogenesis of this condition. He points out that the lesion is usually located in the region of the medial malleolus, the most distal point of the great saphenous system. In this site hydrostatic pressure and stagnation of fluid in the tissues are most marked in the presence of varicosities of the great saphenous vein. In addition, the exposed ankle is prone to minor trauma which frequently initiates the ulcer. The fact that the stagnant blood is oxygen poor and metabolite rich, when compared with blood removed from normal veins in the lower limb, is probably also important in reducing the resistance of the skin. Since superficial thrombophlebitis is a common occurrence in patients with long-standing varicose veins, the additional local phlebitis and lymphedema thus imposed upon an area of chronic stasis frequently act as the exciting factor in the production of the ulcer.

The author points out that once an ulcer starts, it almost invariably becomes infected. As a result, cellular infiltration occurs in the region of the margin and base of the ulcer and is followed by fibrosis and cicatrical contraction of the tissues. This latter reaction produces a reduction in local capillary and arteriolar blood supply.

With regard to treatment, the author is in favor of preliminary high ligation and division of the great saphenous vein, even before the ulcer is clean. It is his belief that the operation frequently shortens the period of pain and disability to a great extent. When dermatitis is present, resulting from stasis in the skin, bed rest for a short period of time, elevation of the extremity, and the application of Burow's solution, 1:20 strength, will usually clear up the condition. When considerable infection or epidermophytosis is present as a complicating factor, wet dressings of potassium permanganate 1:5,000 applied for a few days at the beginning of treatment are efficacious.

As soon as the skin clears and edema is reduced, ambulatory treatment is instituted. The author found that Daxalan, a proprietary substance composed of crude cold tar, zinc oxide, starch, and petrolatum as a base, was of considerable use in combatting local infection in the ulcer and stimulated healing. This ointment is applied to the ulcer after the skin has been cleansed, unscented talcum powder is sprinkled on the surface of the ointment, and a smooth, evenly applied Dome boot, a modified Unna's paste boot, is placed on the limb from the toes to the knee. The patient is instructed to return in one week. During this interval he is encouraged to be ambulant. After a week the boot is cut, the ulcer and surrounding skin cleansed with mineral oil, and a second application of Daxalan ointment, talcum powder, and Dome boot is made. This time the boot is allowed to remain on the limb for two weeks. The same routine is repeated until the ulcer is firmly healed.

The author has treated 147 subjects with chronic leg ulcers with this regimen and found the results wholly satisfactory as an ambulatory method of therapy. The maximal period of time required to effect a cure was ten weeks and the minimum, two weeks. Since two patients in the series were found to be sensitive to Daxalan, it is the author's opinion that a patch test should be done on each individual before beginning treatment, using an area of diseased skin. It is also necessary to avoid exposure to direct sunlight of the surface to which the ointment is applied or has recently been applied, since tar is a photosensitizer. Furthermore, prolonged use of the ointment on hairy areas may cause folliculitis. ABRAMSON.

**Boger, W. P., Miller, A. K., Tillson, E. K., and Shaner, G. A.: Caronamide: Plasma Concentrations, Urinary Recoveries, and Dosage.** J. Lab. & Clin. Med. **33**:297 (March), 1948.

The purpose of this paper is to report the plasma concentration following various doses of Caronamide by the oral and parenteral route of administration, the amount recovered in the urine, and the correlation of simultaneously determined Caronamide and penicillin plasma concentration.

It was found that in order to obtain at least a two-fold elevation of penicillin plasma concentration, it was necessary to maintain a Caronamide plasma concentration of approximately 15 mg. per 100 cubic centimeters. A single oral dose of 4.0 Gm. of Caronamide will not maintain this concentration in the plasma but, by reason of partial inhibition of the renal tubules, will influence penicillin excretion from four to five hours. In some patients 1.5 Gm. of Caronamide every three hours raised the Caronamide plasma level to 15 mg. per 100 cubic centimeters. In the majority of patients, however, 3.0 Gm. every three hours or 4.0 Gm. every four hours were required in order to maintain critical levels. Caronamide plasma concentrations of 20 to 40 mg. per 100 c.c. are well tolerated and probably represent the concentrations that maximally inhibit the tubular excretion of penicillin. There are marked individual differences in the metabolism of this compound, but the average twenty-four hour recovery of free Caronamide is 35.8 per cent and of Caronamide and its metabolic products, 47.26 per cent of the material injected.

A simple and reliable method for Caronamide determination is described which permits the individualization of Caronamide dosage. KLINE.

**Davison, S.: Spontaneous Rupture of a Papillary Muscle of the Heart.** J. Mt. Sinai Hosp. **14**:941 (March-April), 1948.

Spontaneous rupture of a papillary muscle of the heart is rare. Twenty cases were recorded in the literature up to 1935, and since that year six others have been reported. To this group three cases have been added by the author. One of these is the first recorded case where a clinical ante-mortem diagnosis was made.

In the great majority of the cases reviewed, spontaneous rupture of the papillary muscle was secondary to coronary artery occlusion and associated myocardial infarction. In several instances, however, thrombosis of a coronary artery was not demonstrated and arteriosclerosis of the coronary arterial tree was minimal. In this connection the concept of coronary insufficiency is pertinent. It has been shown that in coronary insufficiency the pathologic myocardial alterations are characteristic and consist mainly of focal or diffusely mottled or hemorrhagic areas in the subendocardial region of the left ventricle. The papillary muscles, particularly the posterior, show the predominant lesions. Furthermore, the papillary muscles do comparatively more work than other portions of the myocardium and react more readily to oxygen lack. These considerations suggest that coronary insufficiency may be the common denominator in instances of spontaneous papillary muscle rupture, with or without coronary artery occlusion.

The diagnosis of this cardiac catastrophe should be considered in any patient who has suffered a recent myocardial infarction accompanied by the development of a new murmur or with a change in the character and intensity of a murmur which antedated the infarction. The murmur is usually mitral in position, systolic in time, and becomes loud and harsh at the time of rupture. In addition there is usually a sudden radical change in the patient's condition, sudden death occurring not infrequently. This condition must be differentiated from a ruptured mitral chordae tendineae, rupture of an aortic cusp, and acute perforation of an infarcted interventricular septum. KLINE.

**Cleland, W. P.: Cavernous Haemangioma of the Lung: Report of a Case.** Thorax 3:48 (March), 1948.

The author reports the case of a woman, 51 years of age, who as a child had always been breathless and blue and was under constant observation for "heart trouble." Her father also had been similarly affected. She married while a young woman and had three children without undue difficulty. For several years preceding her death, her symptoms had become worse, and, in addition, she noticed undue fatigue, a winter cough associated with some sputum, and severe epistaxes recurring at almost weekly intervals. Six months before her demise she was admitted to the hospital where a diagnosis of pulmonary hemangioma with cardiac failure was made; the latter responded to rest and routine measures. She was later admitted for removal of the hemangioma of the lung. At this time the findings included intense cyanosis combined with multiple small hemangiomata on the face, eyelids, lips, buccal mucosa, nasal septum, base of the nails, and tongue. The heart was not clinically enlarged, and there were no cardiac murmurs. The blood pressure was 130/70. Over the base of the right lung there was a loud but fairly localized to-and-fro murmur, accompanied by a thrill. Angiocardiography showed the dye passing through a dilated right pulmonary artery into the lobulated tumor in the right lower lobe and back to the heart through a dilated pulmonary vein. It also demonstrated the vascular nature of the tumors in the left lung.

A lower lobectomy was performed without incident. Her general condition immediately after the operation was good. Some twelve hours after its conclusion, however, the pulse began to rise and the blood pressure to fall, and in spite of various measures her condition rapidly deteriorated and she died about twenty hours after the operation. Adequate cause of death was not found at autopsy. KLINE.

**Dontigny, P., Hay, E. C., Prado, J. L., and Selye, H.: Hormonal Hypertension and Nephrosclerosis as Influenced by the Diet.** Am. J. M. Sc. 215:442 (April), 1948.

Previous work established the fact that treatment of rats with lyophilized anterior pituitary substance (LAP) leads, under certain experimental conditions, to characteristic renal and cardiovascular lesions which are similar to those produced by desoxycorticosterone acetate (DCA) or by various chronic, nonspecific stresses. The renal lesions are mainly characterized by enlargement and hyalinization of the glomeruli, formation of hyaline casts, dilatation of the renal tubules, and thickening and hyaline necrosis of arteriolar walls. These pathologic modifications are considered to be similar to those described in the malignant type of arterial hypertension, and are referred to as nephrosclerosis.

Various further studies of the factors involved in the LAP nephrosclerosis are presented in this report. It was found that a pronounced degree of hypertension occurs in a high percentage of the animals, but that this can be prevented (as well as the development of nephrosclerosis) by administration of a diet containing a minimum amount of protein (about 15 per cent). Five vitamins of the B group, including thiamin, riboflavin, pyridoxine, and calcium pantothenate, were inactive against the hypertension and nephrosclerosis, but choline chloride had a slight beneficial effect if given in excessive amounts (1.0 Gm. per 100 Gm. food). A very pronounced adrenal enlargement was always present in the hypertensive rats. Control animals on 15 per cent and 30 per cent casein diets showed no significant difference in adrenal weight, but in LAP-treated animals there was a very significant difference between adrenal weights in animals on low and high protein intakes.

Experiments now under way show that the hypertension produced by DCA is not influenced by diet in the same drastic manner as the LAP hypertension; animals receiving large doses of DCA develop nephrosclerosis and hypertension of almost equal intensity on diets containing 15 per cent or 30 per cent casein. This seems to indicate that the part played by the high-protein diet in the LAP hypertension results predominantly from the fact that it permits a pronounced enlargement of the suprarenal gland. DURANT.

# American Heart Association, Inc.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

## GRANTS FOR RESEARCH IN CARDIOVASCULAR DISEASE BY THE AMERICAN HEART ASSOCIATION

The American Heart Association announces that applications for fellowships and for research in cardiovascular disease are available. Application blanks may be obtained by addressing Medical Director, American Heart Association, 1775 Broadway, New York 19, N. Y.

The ultimate aim of the American Heart Association is to develop a continuing program of productive research within the broad field of diseases of the heart and blood vessels.

The recommendations of the Research Policy Committee were published in the American Heart Journal **36**: 463, September, 1948. These policies are subject to modification by the membership of the Scientific Council of the American Heart Association and approval by the Board of Directors.

The research program of the American Heart Association will be closely coordinated with that of the National Heart Institute of the National Institute of Health, United States Public Health Service and with the Life Insurance Medical Research Fund.

## EXECUTIVE SECRETARIES OF LOCAL HEART ASSOCIATIONS HOLD FIRST NATIONAL CONFERENCE

The first National Conference of Executive Secretaries of local heart associations affiliated with the American Heart Association was held on October 19 and 20 at the Henry Hudson Hotel in New York City. Representatives of thirty-five local heart associations attended the conference.

Plans were discussed for the development of standards for cardiac clinics, employment and rehabilitation programs, educational methods and materials, local rheumatic fever programs, and community relationships.

Plans for cooperation of the newly created National Heart Institute of the United States Public Health Service with the program of the American Heart Association and its local affiliates were discussed by speakers representing both agencies.

A. W. Robertson, Chairman of the Board of the American Heart Association, presided at one session at which the fund-raising and publicity plans for the forthcoming campaign were reviewed. Speakers at the two-day meeting included Dr. H. M. Marvin, President-Elect of the American Heart Association; Dr. Charles A. R. Connor, Medical Director of the Association; Judson Hardy, Chief of the Office of Scientific Reports, National Institute of Health, United States Public Health Service; Lealon E. Martin, Jr., Chief, Heart Information Center, National Heart Institute.

## WILLIAM E. COTTER EXECUTIVE VICE-CHAIRMAN OF 1949 NATIONAL CAMPAIGN

William E. Cotter, Counsel for the Union Carbide & Carbon Corp., New York, has been named Executive Vice-Chairman for the Association's 1949 National Campaign. Mr. Cotter will work with Harold E. Stassen, National Campaign Chairman, in directing the national campaign activities.

Mr. Cotter has held many executive positions in health and welfare organizations, including the American Red Cross, War Loan Drives, United China Relief, the USO, the National War Fund, New York University-Bellevue Medical Center Fund, the Lay Committee for Financing Medical Education, the Occupational Research Foundation, and the Greater New York Fund.

## ADDITIONS TO NATIONAL CAMPAIGN COMMITTEES

Since the November issue of the American Heart Journal went to press with incomplete membership lists of the 1949 National Campaign Planning Committee and the National Sponsors Committee, the following have accepted membership:

### SUPPLEMENTARY LIST

(Since September 28, 1948)

#### CAMPAIGN PLANNING COMMITTEE

Howard S. Cullman, Chairman
Port of New York Authority
New York

Juan T. Trippe, President
Pan American World Airways Corporation
New York

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Edward M. Bernecker, M.D., Commissioner
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Louisville, Ky.

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Bristol-Myers Company
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Prescott S. Bush
Brown Brothers Harriman & Company
New York

Rear Admiral Richard E. Byrd
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Curtis E. Calder, Chairman
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Portland, Ore.

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New York

Lowell Thomas
Pawling, N. Y.

Sinclair Weeks, Chairman
Reed and Barton
Boston

Lewis Allen Weiss, Chairman
Mutual Broadcasting System, Inc.
Hollywood

Mrs. Wendell L. Willkie
New York

## RESEARCH GRANTS AND FELLOWSHIPS TO BE MADE AVAILABLE IN 1949 BY THE LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for grants in aid of research on cardiovascular problems to begin in 1949 will be received by the Life Insurance Medical Research Fund up to Jan. 15, 1949. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems,

as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $500,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1949 to 1950 will be received by this Fund up to January 1, 1949. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.), or the equivalent, is required. The annual stipend varies, as a rule being between $2,500 and $3,500, with larger amounts in special cases. Approximately twelve fellowships will be available.

Later in the year, the Fund will also offer a number of student (pre-doctoral) research fellowships for 1949 to 1950.

Both grants and fellowships will become available on July 1, 1949.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, N. Y.

# INDEX TO VOLUME 36

## AUTHORS INDEX*


A

ABELL, LIESE LEWIS. (*See* Bevans, Kendall, and Abell) (Proc.), 473

ABRAMSON, D. I. (*See* Shumacker, Abramson, and Lampert), 301*

ADELMAN, M. H. Anesthesia in surgery of the patent ductus arteriosus, 316*

ALFREDSON, B. V. (*See* Mullick, Alfredson, and Reineke), 785*

ALLEN, C. R. (*See* Steitzman, Murphy, Allen, and Meek), 311*

ALLEN, E. V. (*See* Brown, Allen, and Craig), 793*

ALSTAD, K. S. Effect of thiocyanate on basal blood pressure, 791*

ALTSCHUL, RUDOLF. New experiments in arteriosclerosis (Proc.), 480

ALTSCHULE, M. D., AND TILLOTSON, K. J. Mechanisms underlying pulmonary and cardiac complications of electrically induced convulsions, 788*

——. (*See* Blumgart and Altschule), 795*

ALVAREZ, G. H. (*See* Padilla, Cossio, Berreta, and Alvarez), 946*

ALZAMORA CASTRO, V. Contribution to the study of S-T changes, angina pectoris, and subendocardic infarctions, 636*

AMROMIN, GEORGE D. (*See* Schlichter, Amromin, and Solway) (Proc.), 479

AMSTERDAM, S. D. (*See* Maliner and Amsterdam), 157*

ARTSIS, N. (*See* Myers and Artsis), 295

ASH, RACHEL. The first ten years of rheumatic infection in childhood, 89

ASHMAN, RICHARD. (*See* Hyman, Failey, and Ashman), 906

AUSCHER, C. (*See* Franck, Grandpierre, Lemaire, and Auscher), 150*

B

BAILLIART, J. (*See* Duguet, Dumont, and Bailliart), 313*

BAKER, J. (*See* Wilens, Elster, and Baker) (Proc.), 478

BAKST, HYMAN, KISSIN, MILTON, LEIBOWITZ, SIDNEY, AND RINZLER, SEYMOUR. The effect of intravenous aminophylline on the capacity for effort without pain in patients with angina of effort, 527

BALDWIN, J. (*See* Cournand, Motley, Himmelstein, Dresdale, and Baldwin), 151*

BARBEN, H. P. (*See* Steinman, Ludi, and Barben), 787*

BARNES, ARLIE R. (*See* Burchell, Pruitt, and Barnes), 373

——. (*See* Flasher, Essex, and Barnes), 882

BATTERMAN, ROBERT C., AND GUTNER, LEONARD B. Hitherto undescribed neurological manifestations of digitalis toxicity, 582

BEAUMONT, G. E., AND HEARN, J. B. A case of reversible papilloedema due to heart failure, 454*

BECK, C. S., PRITCHARD, W. H., AND FEIL, H. S. Ventricular fibrillation of long duration abolished by electric shock, 156*

BECK, DOROTHY FAHS. (*See* Wright, Marple, and Beck), 801

BENN, J. The prognosis of patent ductus arteriosus, 631*

BENO, T. J. (*See* Miale, Millard, Beno, and Custer), 438

BERGMAN, H. C. (*See* Prinzmetal, Corday, Spritzler, and Bergman) (Proc.), 476

——. (*See* Prinzmetal, Ornitz, Simkin, and Bergman), 784*

——. (*See* Prinzmetal, Simkin, Bergman, and Kruger), 790*

BERRETA, J. A. (*See* Padilla, Cossio, Berreta, and Alvarez), 946*

BEVANS, MARGARET, KENDALL, FORREST E., AND ABELL, LIESE LEWIS. Development of atheromatous plaques following production of intimal atherosclerosis by intravenous injection of colloidal cholesterol into rabbits (Proc.), 473

BINET, L., AND BURSTEIN, M. The reaction of the peripheral vascular system of the dog to stimulation of the central end of the vagus nerve, 946*

BINFORD, C. H. (*See* Spicknall and Binford), 452*

BIORCK, G. Ergotamine and apparent coronary insufficiency, 629*

——, GOHLE, O., AND WESTMAN, C. Partial A-V block and duodenal ulcer, 948*

——. (*See* Nylin and Biorck), 150*

BIRCHALL, ROBERT. (*See* Taylor, Birchall, Corcoran, and Page), 221

BLACKFORD, L. M. Calcification of the myocardium, 302*

BLAIN, ALEXANDER, III, CAMPBELL, KENNETH N., AND HARRIS, BRADLEY M. Sympathectomy for arteriosclerosis obliterans rationale and results (Proc.), 477

BLECHA, ELMIRA. (*See* Wilkinson, Jr., Blecha, and Reimer) (Proc.), 472


*An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

BLOCH, KONRAD. Some aspects of the intermediary metabolism of cholesterol (Proc.), 471

BLUMGART, H. L., AND ALTSCHULE, M. D. Clinical significance of cardiac and respiratory adjustments in chronic anemia, 795*

——, FREEDBERG, A. S., ZOLL, P. M., LEWIS, H. D., AND WESSLER, S. The effect of Dicumarol on the heart in experimental acute coronary occlusion, 13

BODNAR, ST. R. (*See* Guest, Murphy, Bodnar, Ware, and Seegers), 152*

BOGER, W. P., MILLER, A. K., TILLSON, E. K., AND SHANER, G. A. Caronamide: plasma concentrations, urinary recoveries, and dosage, 955*

BORISON, H. L. (*See* Wang and Borison), 460*, 461*

BOYLE, M. N. (*See* Wegria and Boyle), 793*

BRANNAN, D. D. (*See* Nichol and Brannan), 634*

BRANNON, E. S. Hemiplegia following carotid sinus stimulation, 299

——. (*See* Warren, Brannon, Weens, and Stead, Jr.), 455*

BRAUN, K. (*See* Rachmilewitz and Braun), 284

BREGANTE, L. J. The augmentation of the effects of vagal stimulation upon the auricular muscle of the turtle by veratrine and sulfocyanate, 945*

BRODEN, B., HANSON, H. E., AND KARNELL, J. Thoracic aortography, 948*

BROWN, H. S., ALLEN, E. V., AND CRAIG, W. McK. The effect of tetraethylammonium chloride on blood pressure before and after sympathectomy for hypertension, 793*

BROWN, WILSON G. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox), 334

——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Cont'd), 481

——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Concl'd), 683

BURCH, G., AND RAY, T. Cardiovascular system as the effector organ in psychosomatic phenomena, 943*

BURCHELL, HOWARD B., PRUITT, RAYMOND D., AND BARNES, ARLIE R. The stress and the electrocardiogram in the induced hypoxemia test for coronary insufficiency, 373

——. (*See* Montgomery, Jr., Wood, Burchell, Dry, Parker, and Helmholz, Jr.), 668

BURGE, JULIUS C., JR. (*See* Levine and Burge, Jr.), 431

BURSTEIN, M. (*See* Binet and Burstein), 946*

BUTTERWORTH, J. SCOTT, AND POINDEXTER, CHARLES A. A multiple channel electronic stethoscope for teaching and demonstration, 112

C

CABRERA, E., AND SODI-PALLARES, D. Discussion of the circus movement: proof of its occurrence in the clinical auricular flutter, 635

CAMPBELL, KENNETH N. (*See* Blain, III Campbell, and Harris) (Proc.), 477

CANTONNET, P., AND MILOVANOVICH, J. B. Two- and three-dimensional electrovectography, 150*

CARTER, F. B. (*See* Ross, Lambeth, Thomas, and Carter), 795*

CASSELS, D. E. (*See* Morse, Cassels, and Schlutz), 634*

CECIL, RICHARD C., PARKER, CARL P., JR., AND PORTER, WILLIAM B. Bacterial endocarditis, 934

CHANEY, ALBERT L. (*See* Morrison, Chaney, Langmade, and Johnson) (Proc.), 474

CHARDON, G., GROSS, A., AND FOURRIER, A. On the cause of cardiac acceleration during anoxia, 946*

CHARLIER, R., AND PHILIPPOT, E. Heart and carotid sinus. II. Endo-sinusal hypotension and right ventricular pressure. III. Endo-sinusal hypotension and cardiac dynamics in the sympathectomized and in the completely denervated heart of dogs, 946*

——. The role of the carotid sinus and the cardioaortic region in reflex regulation of cardiac output, 949*

CHIEFFI, MARGARET. (*See* Kountz, Chieffi, and Kirk) (Proc.), 475

CISNEROS, F. (*See* Wiburne, Schlichter, Grossman, and Cisneros), 153*

CLARK, J. H. (*See* Nelson, Mayerson, Clark, and Lyons), 308*

CLELAND, W. P. Cavernous hemangioma of the lung, 956*

CLERC, A., AND QUINCAUD, A. Identical electrocardiograms with cardiac apex formed by right or left ventricular myocardium, 949*

COOPER, B. J. (*See* Gruhzit, Fisken, and Cooper), 792*, 952*

COOPER, F. W., JR., HARRIS, M. H., AND KAHN, J. W. Ligation and division of the abdominal aorta for metallic embolus from the heart, 950*

COOPER, W. M. Treatment of varicose ulcer, 954*

CORCORAN, A. C. (*See* Taylor, Birchall, Corcoran, and Page), 221

——, TAYLOR, R. D., AND PAGE, IRVINE H. Circulatory responses to spinal and caudal anesthesia in hypertension: relation to the effect of sympathectomy. II. Effect on renal function, 226

CORDAY, ELIOTT. (*See* Jaffe, Corday, and Master), 911

——. (*See* Prinzmetal, Corday, Spritzler, and Bergman) (Proc.), 476

COSSIO, P., DAMBROSI, R. G., AND WARNFORD-THOMSON, H. T. The first heart sound in auricular and ventricular extrasystoles, 630*

——. (*See* Padilla, Cossio, Berreta, and Alvarez), 946*

COURNAND, A., MOTLEY, H. L., HIMMELSTEIN, A., DRESDALE, D., AND BALDWIN, J. Recording of blood pressure from the left auricle and the pulmonary veins

in human subjects with interauricular septal defects, 151*
——. (*See* Motley, Cournand, Werkö, Himmelstein, and Dresdale), 152*
COURNAND, ANDRÉ. (*See* Ferrer, Harvey, Werkö, Dresdale, Cournand, and Richards, Jr.), 816
COX, N. Cardiac murmurs in infancy, 787*
CRAIG, W. McK. (*See* Brown, Allen, and Craig), 793*
CROCKET, K. A., AND RHOADS, P. S. Hyperthermia caused by penicillin-heparin in the treatment of subacute bacterial endocarditis, 790*
CRUTCHER, R. R., AND DANIEL, R. A., JR. Pulmonary embolism, 789*
CUSTER, G. S. (*See* Miale, Millard, Beno, and Custer), 438

D

DAMBROSI, R. G. (*See* Cossio, Dambrosi, and Warnford-Thomson), 630*
DANIEL, R. A., JR. (*See* Crutcher and Daniel, Jr.), 789*
DANKNER, A. (*See* Glaser, Dankner, Mathes, and Harford), 302*
DANOWSKI, T. S., WINKLER, A. W., AND ELKINTON, J. R. Biochemical and hemodynamic changes following the subcutaneous injection of glucose solution, 308*
DAVIDSON, J. D. (*See* Steiner, Davidson, and Kendall) (Proc.), 477
DAVIS, WILLIAM H. The clinical diagnosis of arteriosclerosis (Proc.), 473
DAVISON, S. Spontaneous rupture of a papillary muscle of the heart, 955*
DENOLIN, H. (*See* Lequine, Denolin, and Verniory), 949*
——. (*See* Segers, Vastesaeger, and Denolin), 944*
DOANE, JOSEPH C., AND KRASNOFF, SIDNEY O. Extreme bradycardia, 777
DONIACH, I. Uremic edema of the lungs, 310*
DONTIGNY, P., HAY, E. C., PRADO, J. L., AND SELYE, H. Hormonal hypertension and nephrosclerosis as influenced by the diet, 956*
DRAPER, A. J., JR. Dicumarol poisoning, 454*
DRESBACH, M. Further experiments in an attempt to locate the site of the emetic action of the digitalis glycosides, 156*
DRESDALE, D. (*See* Cournand, Motley, Himmelstein, Dresdale, and Baldwin), 151*
——. (*See* Motley, Cournand, Werkö, Himmelstein, and Dresdale), 152*
DRESDALE, DAVID T. (*See* Ferrer, Harvey, Werkö, Dresdale, Cournand, and Richards, Jr.), 816
DRESSLER, WILLIAM, AND ROESLER, HUGO. The diagnostic value of the pattern $T_1$ lower than $T_3$ ($T_1 < T_3$) compared with the information yielded by multiple chest leads in myocardial infarction, 115
DRY, THOMAS J. (*See* Montgomery, Jr., Wood, Burchell, Dry, Parker, and Helmholz, Jr.), 668
DUFF, G. LYMAN, AND MCMILLAN, GARDNER, C. The inhibition of experimental cholesterol atherosclerosis by alloxan diabetes in the rabbit (Proc.), 469
DUGUET, J., DUMONT, P., AND BAILLIART, J. The effects of anoxia on retinal vessels and retinal arterial pressure, 313*
DUMONT, P. (*See* Duguet, Dumont, and Bailliart), 313*

E

EASTMAN, WILLIAM. (*See* Gerber, McCune, and Eastman) (Proc.), 478
ECKENHOFF, JAMES E., AND HAFKENSCHIEL, JOSEPH H. The oxygen content of coronary venous blood as affected by anoxia and cytochrome C, 893
ECKENHOFF, J. E., AND HAFKENSCHIEL, J. H. The effect of nikethamide on coronary blood flow and cardiac oxygen metabolism, 156*
EDWARDS, JESSE E. (*See* Rogers and Edwards), 28
ELKINGTON, J. R. (*See* Danowski, Winkler, and Elkington), 308*
ELMQUIST, A., AND RYDIN, H. The influence of muscular exercise on the tolerance of digitalis in guinea pigs, 948*
ELSTER, S. (*See* Wilens, Elster, and Baker), 478
ENGEL, G. L., AND ROMANO, J. Studies of syncope. IV. Biologic interpretation of vasodepressor syncope, 309*
ESPERSEN, T., AND JORGENSEN, J. Electrocardiographic changes in paroxysmal hypertension due to chromaffin adrenal tumor, 150*
ESSEX, HIRAM E. (*See* Flasher, Essex, and Barnes), 882
EYSTER, J. A. E., AND GILSON, W. E. Electrical characteristics of injuries to heart muscle, 153*

F

FABER, M. (*See* Hansen and Faber), 153*, 460*
FABRICIUS, B. Kymographic studies of the function of the auricle, 949*
FAILEY, R. B. (*See* Hyman, Failey, and Ashman), 906
FARAH, A., AND MARESH, G. Determination of the therapeutic irregularity and lethal doses of cardiac glycosides in the heart-lung preparation of the dog, 452*, 950*
——, AND ——. The influence of sulfhydryl compounds on diuresis and renal and cardiac circulatory changes caused by mersalyl, 452*, 950*
FAUTEUX, M. Cardiac resuscitation, 947*
FAWCETT, R. M. Myocardium after sulfonamide therapy, 304*
FEIL, HAROLD. (*See* Jones and Feil), 98, 739
FEIL, H. S. (*See* Beck, Pritchard, and Feil), 156*
FERRER, M. IRENÉ, HARVEY, REJANÉ M., WERKÖ, LARS, DRESDALE, DAVID T., COURNAND, ANDRÉ, AND RICHARDS, DICKINSON, W., JR. Some effects of

quinidine sulfate on the heart and circulation in man, 816
FEUCHTWANGER, J. L. Arteriography of the limbs, 154*
FISHMAN, W. H. (*See* LeVeen and Fishman), 632*
FISKEN, R. A. (*See* Gruhzit, Fisken, and Cooper), 792*, 952*
FITZGERALD, RICHARD P. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox), 334
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Cont'd), 481
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Concl'd), 683
FLASHER, JACK, ESSEX, HIRAM E., AND BARNES, ARLIE R. An experimental study of acute pulmonary arterial obstruction, with special reference to the precordial electrocardiogram, 882
FOURRIER, A. (*See* Chardon, Gross, and Fourrier), 946*
FRANCK, C., GRANDPIERRE, R., AND ROYER, P. Transitory apnea in man induced by breathing a mixture rich in oxygen during a state of anoxemia, 949*
——, ——, LEMAIRE, R., AND AUSCHER, C. The effect of anoxia on adrenalin induced hyperglycemia, 150*
FREEDBERG, A. S. (*See* Blumgart, Freedberg, Zoll, Lewis, and Wessler), 13
FREEMAN, A. M. Acute postpartal heart failure; a report of four cases with an inquiry into pathogenesis, 312*
FREEMAN, N. E., LEEDS, F. H., AND GARDNER, R. E. Sympathectomy for obliterative arterial disease: indications and contraindications, 635*
FREIS, EDWARD D., AND STANTON, JOSEPH R. A clinical evaluation of veratrum viride in the treatment of essential hypertension, 723
FULTON, JOAN B. (*See* Simms, Parshley, Pitt, and Fulton), 469

G

GARDNER, R. E. (*See* Freeman, Leeds, and Gardner), 635*
GEISLER, MURRAY A. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox), 334
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Cont'd), 481
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Concl'd), 683
GERBER, LEON, MCCUNE, WILLIAM S., AND EASTMAN, WILLIAM. Lumbar ganglionectomy in peripheral arteriosclerosis (Proc.), 478
GILSON, W. E. (*See* Eyster and Gilson), 153*
GLASER, R. J., DANKNER, A., MATHES, S. B., AND HARFORD, C. G. Effect of penicillin on the bacteremia following dental extraction, 302*
GODFREY, J. Thoracic tenderness in pulmonary infarction, 788*
GOHLE, O. (*See* Biorck, Gohle, and Westman), 948*
GOLDBERGER, EMANUEL. A simple method of determining abnormalities of the Q-T interval, 141
GONZALES, WILLIAM. (*See* Morrison, Hall, and Gonzales) (Proc.), 474
GONZALES, WILLIAM F. (*See* Morrison and Gonzales), 473
GOODMAN, M. J. Periarteritis nodosa with recovery; report of an unusual case apparently due to sensitivity to sulfadiazine, 451*
GORE, I. Myocardial changes in fatal diphtheria, 953*
GORE, IRA, AND SAPHIR, OTTO. Myocarditis associated with acute and subacute glomerulonephritis, 390
GRAHAM, G. (*See* Wiggers, Levy, and Graham), 631*
GRANDPIERRE, R. (*See* Franck, Grandpierre, and Royer), 949*
——. (*See* Franck, Grandpierre, Lemaire, and Auscher), 150*
GRANGER, H. R. (*See* Siegmund, Nash, and Granger), 943*
GRAYSON, C. (*See* Wendholz and Grayson), 309*
GRAYSON, C. E. Cardiac calcifications, annular and valvular (leaflet), 794*
GRAYZEL, D. M. (*See* Loewe, Hirsch, and Grayzel), 312*
GREGERSON, M. I. (*See* Root, Walcott, and Gregerson), 632*
GREGG, D. E., AND SHIPLEY, R. E. Studies of the venous drainage of the heart, 631*
GREISMAN, HARRY, AND MARCUS, RAYMOND M. Acute myocardial infarction: detailed study of Dicumarol therapy in seventy-five consecutive cases, 600
GRISWOLD, R. A. (*See* Maguire and Griswold), 311*
GROLLMAN, A. Effect of pregnancy on course of experimental hypertension, 634*
GROSS, A. (*See* Chardon, Gross, and Fourrier), 946*
GROSSMAN, M. (*See* Wilburne, Schlichter, Grossman, and Cisneros), 153*
GRUBER, C. M., AND KEYSER, G. F. The effects of analgesic drugs upon excised frog and terrapin cardiac vagus nerve, 930*
GRUHZIT, O. M., FISKEN, R. A., AND COOPER, B. J. Tetraethylammonium chloride; acute and chronic toxicity in experimental animals, 952*
——, ——, AND ——. Tetraethylammonium chloride ($N(C_2H_5)_4NCl$), 792*
GUBERGRITS, A. Y. Occult injuries to the heart, 316*
GUBNER, RICHARD. (*See* Ungerleider and Gubner) (Proc.), 474
GUEST, M. M., MURPHY, R. C., BODNAR, ST. R., WARE, A. G., AND SEEGERS, W. H. Physiological effects of a plasma protein: blood pressure, leucocyte concentration, smooth and cardiac muscle activity, 152*
GUTNER, LEONARD B. (*See* Batterman and Gutner), 582

H

HADOT, E. (*See* Mathieu and Hadot), 151*
HAFKENSCHIEL, J. H. (*See* Eckenhoff and Hafkenschiel), 156*
HAFKENSCHIEL, JOSEPH H. (*See* Eckenhoff and Hafkenschiel), 893
HAGEDORN, A. B. (*See* Scheifley and Hagedorn), 453*
HALL, LILLIAN. (*See* Morrison, Hall, and Gonzales) (Proc.), 474
HAND, A. Cerebral abscess; a complication of congenital cardiac disease (Fallot's tetralogy), 301*
HANSEN, P., AND FABER, M. Raynaud's syndrome originating from reversible precipitation of protein, 153*, 460*
HANSON, H. E. (*See* Broden, Hanson, and Karnell), 948*
HARFORD, C. G. (*See* Glaser, Dankner, Mathes, and Harford), 302*
HARKEN, D. E. The removal of foreign bodies from the pericardium and heart: a moving picture demonstration, 947*
HARRIS, A. S., AND MATLOCK, W. P. The effects of anoxemic anoxia on excitability, conduction, and refractoriness of mammalian cardiac muscle, 152*
HARRIS, BRADLEY M. (*See* Blain, III, Campbell, and Harris) (Proc.), 477
HARRIS, M. H. (*See* Cooper, Jr., Harris, and Kahn), 950*
HARVEY, REJANÉ M. (*See* Ferrer, Harvey, Werkö, Dresdale, Cournand, and Richards, Jr.), 816
HAY, E. C. (*See* Dontigny, Hay, Prado, and Selye), 956*
HAYWARD, G. W. Tetraethyl ammonium bromide in hypertension and hypertensive heart failure, 453*
HAZELTON, A. R. (*See* Leigh and Hazelton), 310*
HEARN, J. B. (*See* Beaumont and Hearn), 454*
HEINBECKER, P. (*See* White, Heinbecker, and Rolf), 633*
HEJTMANCIK, M. R., AND HERRMANN, G. R. Paroxysmal ventricular tachycardia with special reference to treatment, 636*
HELLERSTEIN, HERMAN K. Atrial infarction with diagnostic electrocardiographic findings, 422
HELLERSTEIN, H. K., AND KATZ, L. N. The electrical effects of injury at various myocardial locations, 184
——. (*See* Wartman and Hellerstein), 317*
HELMHOLZ, H. FREDERIC, JR. (*See* Montgomery, Jr., Wood, Burchell, Dry, Parker, and Helmholz, Jr.), 668
HENDRY, W. G. Superior mesenteric arterial occlusion—recovery without resection, 787*
HENSCHEL, A. (*See* Taylor, Henschel, and Keys), 785*
HERNÁNDEZ-MORALES, FEDERICO. (*See* Suárez, Santiago-Stevenson, and Hernández-Morales), 923
HERNBERG, C. A. Myocardial affection in malaria tertiana, 154*
HERRMANN, G. R. (*See* Hejtmancik and Herrmann), 636*
HIMMELSTEIN, A. (*See* Cournand, Motley, Himmelstein, Dresdale, and Baldwin), 151*
——. (*See* Motley, Cournand, Werkö, Himmelstein, and Dresdale), 152*
HIRATZKA, TOMIHARU. (*See* Myers, Klein, and Hiratzka), 838
HIRSCH, E. (*See* Loewe, Hirsch, and Grayzel), 312*
HOLMAN, RUSSELL L. Studies on the relationship of diet and renal insufficiency to arterial disease (Proc.), 476
HOLMES, R. B. (*See* Paterson and Holmes), 470
HORGER, EUGENE L. (*See* Stewart, Horger, and Sorenson), 161
HORLICK, LOUIS, KATZ, LOUIS N., AND STAMLER, JEREMIAH. The effect of a low fat diet on the spontaneously occurring arteriosclerosis of the chicken (Proc.), 472
HULL, EDGAR, TUCKER, HERBERT DE N., AND WEILBAECHER, J. O., JR. False abnormality of precordial electrocardiograms due to the effect of changes of potential at the remote electrode, 135
HUMPHREYS, E. M. The cardiac lesions of acute disseminated lupus erythematosus, 786*
HURST, W. W., AND SCHEMON, F. R. High ventricular septal defect with slight dextroposition of the aorta (Eisenmenger type) which presented the clinical features of patent ductus arteriosus, 144
HYMAN, ALBERT, FAILEY, R. B., AND ASHMAN, RICHARD. Can the longitudinal anatomical axis of the ventricles be estimated from the electrocardiogram? 906

J

JAFFE, HARRY L., CORDAY, ELIOTT, AND MASTER, ARTHUR M. Evaluation of the precordial leads of the electrocardiogram in obesity, 911
JOHNSON, W. A. (*See* Morrison, Chaney, Langmade, and Johnson) (Proc.), 474
JONES, A. MORGAN, AND FEIL, HAROLD. On axis deviation in human bundle branch block, 98
——, AND ——. The effect of posture upon axis deviation in human bundle branch block, 739
JORGENSEN, J. (*See* Espersen and Jorgensen), 150*

K

KAGAN, B. M., AND MIRMAN, B. Sydenham's chorea, a syndrome for differential diagnosis, 154*
KAHN, J. W. (*See* Cooper, Jr., Harris, and Kahn), 950*
KALDECK, R. Transient hemiplegia following electroconvulsive treatment, 952*
KARNELL, J. (*See* Broden, Hanson, and Karnell), 948*

KATZ, L. N. (*See* Hellerstein and Katz), 184
KATZ, LOUIS N. (*See* Horlick, Katz, and Stamler) (Proc.), 472
KEMPNER, W. Treatment of hypertensive vascular disease with rice diet, 794*
KENDALL, FORREST E. (*See* Bevans, Kendall, and Abell) (Proc.), 473
——. (*See* Steiner, Davidson, and Kendall) (Proc.), 477
KEYS, A. (*See* Taylor, Henschel, and Keys), 785*
KEYSER, G. F. (*See* Gruber and Keyser), 950*
KIRK, ESBEN. (*See* Kountz, Chieffi, and Kirk) (Proc.), 475
KISCH, BRUNO. (*See* Roth and Kisch), 257
KISSIN, MILTON. (*See* Bakst, Kissin, Leibowitz, and Rinzler), 527
KLEIN, HOWARD A. (*See* Myers, Klein, and Hiratzka), 838
——. (*See* Myers, Klein, and Stofer), 535
KLEMPERER, P. The pathogenesis of lupus erythematosus and allied conditions, 785*
KOUNTZ, WILLIAM B., CHIEFFI, MARGARET, AND KIRK, ESBEN. An evaluation of thyroid function in older individuals with various degrees of arteriosclerosis (Proc.), 475
KRASNOFF, SIDNEY O. (*See* Doane and Krasnoff), 777
KROP, S. (*See* McNamara, Krop, and McKay), 793*, 953*
KRUGER, H. E. (*See* Prinzmetal, Simkin, Bergman, and Kruger), 790*
KYSER, FRANKLIN A., AND TRUMP, RUTH. Further studies on the effect of papaverine upon the cardiotoxic lesions of digitalis in the dog, 133

L

LAMBETH, S. S. (*See* Ross, Lambeth, Thomas, and Carter), 795*
LAMBERT, H. H. (*See* Shumacker, Abramson, and Lampert), 301*
LANGLEY, G. J., AND PLATT, R. Hypertension and unilateral kidney disease, 306*
LANGMADE, CHARLES. (*See* Morrison, Chaney, Langmade, and Johnson) (Proc.), 474
LARKIN, M. A. (Abdominal symptoms in sudden acute heart conditions, 306*
LAVENNE, F. (*See* Lian, Lavenne, and Von Roten), 151*
LAWSON, H. C., OVERBEY, D. T., MOORE, J. C., AND SHADLE, O. W. Mixing of cells, plasma, and dye T-1824 in the cardiovascular system of barbitalized dogs, 633*
——. (*See* Overbey, Moore, Shadle, and Lawson), 633*
LEEDS, F. H. (*See* Freeman, Leeds, and Gardner), 635*
LEFKOVITS, AARON M. Neoplastic metastasis to the heart, 610
LEIBOWITZ, SIDNEY. (*See* Bakst, Kissin, Leibowitz, and Rinzler), 527
LEIGH, E., AND HAZELTON, A. R. Six cases of cardiovascular disorder with peripheral neuritis, 310*
LEITER, L. Renal diseases, 455*
LEMAIRE, R. (*See* Franck, Grandpierre, Lemaire, and Auscher), 150*
LENZI, S. On the Wolff-Parkinson-White syndrome, 308*
LEQUINE, J., DENOLIN, H., AND VERNIORY, A. Dextrocardia and septal defects, 949*
LERICHE, R., AND MOREL, A. The syndrome of thrombotic obliteration of the aortic bifurcation, 951*
LEROY, ELIE P. (*See* Saphir and Leroy), 304*
LEVEEN, H. H., AND FISHMAN, W. H. Combination of Evans blue with plasma protein: its significance in capillary permeability studies, blood dye disappearance curves, and its use as a protein tag, 632*
LEVINE, HAROLD D., AND BURGE, JULIUS C., JR. Septal infarction with complete heart block and intermittent anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome): histologic demonstration of a right lateral bundle, 431
LEVY, M. N. (*See* Wiggers, Levy, and Graham), 631*
LEVY, T. Case report of mechanical right heart failure from extension of an undiagnosed bronchiogenic carcinoma, 312*
LEWIS, H. D. (*See* Blumgart, Freedberg, Zoll, Lewis, and Wessler), 13
LIAN, C., LAVENNE, F., AND VON ROTEN, L. An exercise test in obliterating arterial disease, 151*
LICHTENSTEIN, L., AND SEWALL, S. Pulmonary and cerebral fat embolism following intravenous administration of ether therapeutically, 458*
VAN LIERE, E. J. (*See* Stickney, Northrup, and Van Liere), 152*
LIGHT, F. P. A nine-year follow-up in cases of toxemia of pregnancy, 790*
LINDROTH, L. V. Sympathetic nerve block in hypertension and allied cases, 306*
LIPSCHITZ, W. L., AND STOKEY, E. Diuretic action of formoguanamine in normal persons, 792*, 952*
LOEWE, L., HIRSCH, E., AND GRAYZEL, D. M. The action of heparin on experimental venous thrombosis, 312*
LOGUE, R. B., AND WENDKOS, MARTIN H. Acute pericarditis of benign type, 587
LUDI, H. (*See* Steinmann, Ludi, and Barben), 787*
LYONS, C. (*See* Nelson, Mayerson, Clark, and Lyons), 308*

M

MAECK, J. VAN S., AND ZILLIACUS, H. Heparin in the treatment of toxemia of pregnancy, 790*
MAGUIRE, C. H., AND GRISWOLD, R. A. Further observations on penetrating wounds of the heart and pericardium, 311*
MAINZER, F. Electrocardiographic study of typhoid myocarditis, 944*
MAKINSON, D. H., OLEESKY, S., AND STONE, R. B. Vitamin E in angina pectoris, 788*

MALINER, M. M., AND AMSTERDAM, S. D. Oral penicillin in the prophylaxis of recurrent rheumatic fever, 157*
MARCUS, RAYMOND M. (*See* Greisman and Marcus), 600
MARESH, G. (*See* Farah and Maresh), 452*, 950*
——. (*See* Farah and Maresh), 452*, 950*
MARPLE, CHARLES D. (*See* Wright, Marple, and Beck), 801
MARSH, J. B. (*See* Stadie and Marsh), 155*
MASSEY, F. C., AND WALKER, W. J. Complete atrioventricular block in diphtheritic myocarditis, 786*
MASTER, ARTHUR M. (*See* Jaffe, Corday, and Master), 911
MATHES, S. B. (*See* Glaser, Dankner, Mathes, and Harford), 302*
MATHIEU, L., AND HADOT, E. Myocardial infarction and angina pectoris during serum sickness, 151*
——, AND ——. Obliterating arterial disease of the upper extremity following severe urticaria, 151*
MATLOCK, W. P. (*See* Harris and Matlock), 152*
MAYERSON, H. S. (*See* Nelson, Mayerson, Clark, and Lyons), 308*
MAYNARD, R. M., AND THOMPSON, C. W. Congenital aneurysm of an aortic sinus, 305*
MCALLISTER, W. B. (*See* Waters and McAllister) (Proc.), 475
MCCUNE, WILLIAM S. (*See* Gerber, McCune, and Eastman) (Proc.), 478
MCKAY, E. A. (*See* McNamara, Krop, and McKay), 793*
——. (*See* McNamara, Krop, and McKay), 953*
MCKEOWN, F. Acute rheumatism in pregnancy, 792*
MCKINLAY, C. A. Allergic carditis, pericarditis, and pleurisy, 456*
MCMILLAN, GARDNER C. (*See* Duff and McMillan) (Proc.), 469
MCMILLAN, R. L., AND WELFARE, C. R. Chronic auricular fibrillation, 314*
MCNAMARA, B., KROP, S., AND MCKAY, E. A. The effect of calcium on the cardiovascular stimulation produced by acetylcholine, 793*, 953*
MEEK, W. J. (*See* Stutzman, Murphy, Allen, and Meek), 311*
MEILI, E. (*See* Spuhler, Wiesinger, and Meili), 788*
MIALE, J. B., MILLARD, A. L., BENO, T. J., AND CUSTER, G. S. Congenital tricuspid atresia associated with interauricular and interventricular septal defects, 438
MIGLIARO, E. Hypersensitivity of cardiac muscle to potassium ion following the administration of veratrine and sulfocyanate after complete atropinization, 945*
MILLARD, A. L. (*See* Miale, Millard, Beno, and Custer), 438
MILLER, A. K. (*See* Boger, Miller, Tillson, and Shaner), 955*
MILLER, A. T. A re-evaluation of the T-1824 mixing curve, 633*
——. Excretion of the blue dye, T-1824, in the bile, 632*
MILOVANOVICH, J. B. (*See* Cantonnet and Milovanovich), 150*
MIRMAN, B. (*See* Kagan and Mirman), 154*
MONTGOMERY, GEORGE E., JR., WOOD, EARL H., BURCHELL, HOWARD B., DRY, THOMAS J., PARKER, ROBERT L., AND HELMHOLZ, H. FREDERIC, JR. Continuous observations of the arterial oxygen saturation at rest and during exercise in congenital heart disease, 668
MOORE, J. C. (*See* Lawson, Overbey, Moore, and Shadle), 633*
——. (*See* Overbey, Moore, Shadle, and Lawson), 633*
MOREL, A. (*See* Leriche and Morel), 951*
MORELLI, A., AND SALVI, P. Treatment of essential hypertension with vitamin K, 945*
MOREST, F. STANLEY, AND RUBIN, SIDNEY. Embolism at bifurcation of aorta, 277
MORRISON, LESTER M., CHANEY, ALBERT L., LANGMADE, CHARLES, AND JOHNSON, W. A. Studies on the cholesterol content of the coronary arteries and the blood in acute coronary thrombosis (Proc.), 474
——, AND GONZALES, WILLIAM F. The effect of blood cholesterol disorders on the coronary arteries and the aorta (Proc.), 473
——, HALL, LILLIAN, AND GONZALES, WILLIAM. Changes in blood cholesterol levels in patients with coronary occlusion following choline therapy (Proc.), 474
——, AND ROSSI, AMERIGO. Absorption of aortic atherosclerosis by choline feeding (Proc.), 479
——, AND ——. The prevention of experimental atherosclerosis by choline feedings (Proc.), 479
MORSE, M., CASSELS, D. E., AND SCHLUTZ, F. W. Available and interstitial fluid volumes of normal children, 634*
MOTLEY, H. L., COURNAND, A., WERKÖ, L., HIMMELSTEIN, A., AND DRESDALE, D. The influence of short periods of induced acute anoxia upon pulmonary artery pressure in man, 152*
——. (*See* Cournand, Motley, Himmelstein, Dresdale, and Baldwin), 151*
MUFSON, I., QUIMBY, E. H., AND SMITH, B. C. Use of radioactive sodium as a guide to the efficiency of drugs used in treatment of diseases of the peripheral vascular system, 302*
MULLICK, D. N., ALFREDSON, B. V., AND REINEKE, E. P. Influence of thyroid status on the electrocardiogram and certain blood constituents of the sheep, 785*
MUNNELL, W. E., AND TAYLOR, H. C. Liver blood flow in pregnancy—hepatic vein catheterization, 155*

MURPHY, Q. (*See* Stutzman, Murphy, Allen, and Meek), 311*
MURPHY, R. C. (*See* Guest, Murphy, Bodnar, Ware, and Seegers), 152*
MURRAY, G. The tetralogy of Fallot and its surgical treatment, 459*
MUSSAFIA, A. Electrocardiographic and clinical studies on certain types of myocardial infarction: supra-apical, endocardial, epicardial, lateral and anterolateral infarction, 629*
MYERS, GORDON B., KLEIN, HOWARD A., AND HIRATZKA, TOMIHARU. II. Correlation of electrocardiographic and pathologic findings in large anterolateral infarcts, 838
——, ——, AND STOFER, BERT E. I. Correlation of electrocardiographic and pathologic findings in anteroseptal infarction, 535
MYERS, H. L., AND ARTSIS, N. Bilateral nontraumatic iliofemoral thrombophlebitis in a child, 295

N

NASH, V. L. (*See* Siegmund, Nash, and Granger), 943*
NELSON, W., MAYERSON, H. S., CLARK, J. H., AND LYONS, C. Studies of blood volume in tetralogy of Fallot and in other types of congenital heart disease, 308*
NEWMAN, ABBOTT A. (*See* Stewart and Newman), 641
NEWTON, M. (*See* Spealman, Newton, and Post), 153*
NICHOL, A. D., AND BRANNAN, D. D. The differentiation of patent ductus arteriosus and atrial septal defect, 634*
NORTHRUP, D. W. (*See* Stickney, Northrup, and Van Liere), 152*
NYLIN, G., AND BIORCK, G. Circulatory corpuscle and blood volume in a case of patent ductus arteriosus before and after ligation, 150*
——. (*See* Rasmussen and Nylin), 461*

O

OEHNELL, R. F. Pre-excitation and auricular fibrillation, 461*
OLEESKY, S. (*See* Makinson, Oleesky, and Stone), 788*
O'NEILL, J. F. The effects of venous endothelium on alterations in blood flow through the vessels in vein walls, and the possible relation to thrombosis, 462*
OPDYKE, DAVIS F., AND SELKURT, EWALD E. A study of alleged intercoronary reflexes following coronary occlusion, 73
ORNITZ, E. M. (*See* Prinzmetal, Ornitz, Simkin, and Bergman), 784*
OSTLING, G. The significance of the speed of injection for the therapeutic effect of K-strophanthin, 944*
OVERBEY, D. T., MOORE, J. C., SHADLE, O. W., AND LAWSON, H. C. Rate of disappearance of dye T-1824 from arterial blood, 633*
——. (*See* Lawson, Overbey, Moore, and Shadle), 633*

P

PADILLA, T., COSSIO, P., BERRETA, J. A., AND ALVAREZ, G. H. Sympathectomy in essential hypertension, 946*
PAGE, IRVINE H. (*See* Corcoran, Taylor, and Page), 226
——. (*See* Taylor, Birchall, Corcoran, and Page), 221
PAPP, C. (*See* Parkinson and Papp), 629*
PARKER, CARL P., JR. (*See* Cecil, Parker, Jr., and Porter), 934
PARKER, ROBERT L. (*See* Montgomery, Jr., Wood, Burchell, Dry, Parker, and Helmholz, Jr.), 668
PARKINSON, J., AND PAPP, C. Repetitive paroxysmal tachycardia, 629*
PARSHLEY, MARY S. (*See* Simms, Parshley, Pitt, and Fulton) (Proc.), 469
PATERSON, J. C., AND HOLMES, R. B. Hypertension and coronary thrombosis (Proc.), 470
PELLEGRINO, PETER C., AND SILBER, EARL N. Recurrent spontaneous mediastinal emphysema simulating myocardial infarction, 447
PERERA, G. A. Diagnosis and natural history of hypertensive vascular disease, 457*
PHILIPPOT, E. (*See* Charlier and Philippot), 946*
PINCELLI, C. On the behavior of serum cholinesterase in cardiac patients treated with digitalis, 309*
PITT, RUTH B. (*See* Simms, Parshley, Pitt, and Fulton) (Proc.), 469
PLATT, R. Heredity in hypertension, 459*
——. (*See* Langley and Platt), 306*
PLATZ, M. Progress of medical science: nonatheromatous lesions of the coronary arteries, 303*
POINDEXTER, CHARLES A. (*See* Butterworth and Poindexter), 112
POLLACK, ALBERT A., AND WOOD, EARL H. A portable electrical manometer suitable for continuous indication of peripheral venous pressures, 899
POPPE, J. K. Cellophane treatment of syphilitic aneurysms with report of results in six cases, 252
PORTER, WILLIAM B. (*See* Cecil, Parker, Jr., and Porter), 934
POST, R. L. (*See* Spealman, Newton, and Post), 153*
PRADO, J. L. (*See* Dontigny, Hay, Prado, and Selye), 956*
PRINZMETAL, M., ORNITZ, E. M., SIMKIN, B., AND BERGMAN, H. C. Arteriovenous anastomoses in liver, spleen, and lungs, 784*
——, SIMKIN, B., BERGMAN, H. C., AND KRUGER, H. E. Studies on the collateral circulation of the normal human heart by coronary perfusion with radioactive erythrocytes and glass spheres, 790*

PRINZMETAL, MYRON, CORDAY, ELIOTT, SPRITZLER, RAMON, AND BERGMAN, H. C. Radiocardiography: a new method for the study of the circulation (Proc.), 476
PRITCHARD, W. H. (*See* Beck, Pritchard, and Feil), 156*
PRUITT, RAYMOND D. (*See* Burchell, Pruitt, and Barnes), 373

Q

QUIMBY, E. H. (*See* Mufson, Quimby, and Smith), 302*
QUINCAUD, A. (*See* Clerc and Quincaud), 949*

R

RACHMILEWITZ, M., AND BRAUN, K. Electrocardiographic changes in typhoid fever and their reversibility following niacin treatment, 284
RASMUSSEN, H., AND NYLIN, G. The electrocardiogram in mitral stenosis with special regard to its development, 461*
RAVICH, R. M., AND ROSENBLATT, P. Myocardial infarction in the newborn infant, 154*
RAY, T. (*See* Burch and Ray), 943*
REES, C. E. A cause for the reestablishment of communication following ligation of patent ductus arteriosus, 451*
REID, G. Observations on the part played by the vasoconstrictor substance of blood platelets in the mechanism of vascular spasm, 307*
REIMER, ANN. (*See* Wilkinson, Jr., Blecha. and Reimer) (Proc.), 472
REINEKE, E. P. (*See* Mullick, Alfredson, and Reineke), 785*
RHOADS, P. S. (*See* Crocket and Rhoads), 790*
RICH, A. R. A hitherto unrecognized tendency to the development of widespread pulmonary vascular obstruction in patients with congenital pulmonary stenosis (tetralogy of Fallot), 458*
RICHARDS, DICKINSON W., JR. (*See* Ferrer, Harvey, Werkö, Dresdale, Cournand, and Richards, Jr.), 816
RICHTER, ISAAC H., AND TAINSKY, IRVING A. Gangrene of lower extremities in infants, 443
RINZLER, SEYMOUR. (*See* Bakst, Kissin, Leibowitz, and Rinzler), 527
ROBBINS, S. L. (*See* Rogers and Robbins), 157*
ROESLER, HUGO. (*See* Dressler and Roesler), 115
ROGERS, H. MILTON, AND EDWARDS, JESSE E. Incomplete division of the atrioventricular canal with patent interatrial foramen primum (persistent common atrioventricular ostium), 28
ROGERS, J., AND ROBBINS, S. L. Latent rheumatic myocarditis, 157*
ROLF, D. (*See* White, Heinbecker, and Rolf), 633*
ROMANO, F. J.. (*See* Scherf, Romano, and Terranova), 241
ROMANO, J. (*See* Engel and Romano), 309*
ROOT, W. S., WALCOTT, W. W., AND GREGERSON, M. I. Effects of muscle trauma and of hemorrhage upon the cardiac output of the dog, 632*
ROSENBLATT, P. (*See* Ravich and Rosenblatt), 154*
ROSS, COLIN A., AND SPRAGUE, P. H. A case of paradoxical embolism, 772
ROSS, R. A., LAMBETH, S. S., THOMAS, W. L., AND CARTER, F. B. Fifty-four deaths occurring in pregnant patients who had hypertension, 795*
ROSSI, AMERIGO. (*See* Morrison and Rossi) (Proc.), 479
VON ROTEN, L. (*See* Lian, Lavenne, and Von Roten), 151*
ROTH, G. M., AND SHEARD, C. H. Maintenance of vasodilation of the extremities of normal individuals for a prolonged period by the ingestion of two to four substantial meals in close succession, 785*
ROTH, IRVING R., AND KISCH, BRUNO. The mechanism of irregular sinus rhythm in auriculoventricular heart block, 257
ROTH, OSCAR. Coronary occlusion with myocardial infarction following cholecystectomy for relief of anginal pain in a patient with cholelithiasis, 939
ROYER, P. (*See* Franck, Grandpierre, and Royer), 949*
RUBIN, SIDNEY. (*See* Morest and Rubin), 277
RUSSEK, H. I., AND ZOHMAN, B. L. Papaverine in cerebral angiospasm (vascular encephalopathy), 459*
RYDIN, H. (*See* Elmquist and Rydin), 948*

S

SALVI, P. (*See* Morelli and Salvi), 945*
SANTIAGO-STEVENSON, DWIGHT. (*See* Suárez, Santiago-Stevenson, and Hernández-Morales), 923
SAPHIR, OTTO, AND LEROY, ELIE P. True aneurysms of the mitral valve in subacute bacterial endocarditis, 304*
——. (*See* Gore and Saphir), 390
SCHARF, M. M. (*See* Scherf and Scharf), 621
SCHEIFLEY, C. H., AND HAGEDORN, A. B. The treatment of subacute bacterial endocarditis, 453*
SCHEINKER, I. M. Alterations of cerebral capillaries in the early stage of arterial hypertension, 784*
——. Hypertensive cerebral swelling, a characteristic clinico-pathologic syndrome, 457*
SCHEINKER, I. MARK. Cerebral vascular changes in arterial hypertension (Proc.), 470
SCHEMM, F. R. (*See* Hurst and Schemm), 144
SCHENCK, MAX. (*See* Zeman and Schenck) (Proc.), 480
SCHERF, D., ROMANO, F. J., AND TERRANOVA, R. Experimental studies on auricular flutter and auricular fibrillation, 241

SCHERF, DAVID, AND SCHARF, M. M. Supernormal phase of intraventricular conduction, 621
SCHLICHTER, JAKUB G., AMROMIN, GEORGE D., AND SOLWAY, A. J. L. Dissecting aneurysms of the aorta (Proc.), 479
SCHLICHTER, J. G. (*See* Wilburne, Schlichter, Grossman, and Cisneros), 153*
SCHULTZ, F. W. (*See* Morse, Cassels, and Schlutz), 634*
SCHMIDT, E. C. H. Virus Myocarditis, 783*
SCHOENEWALD, G. Treatment of angina pectoris by reduction of basal metabolism, 791*
SCOTT, DAVID H. Aneurysm of the coronary arteries, 403
SEEGERS, W. H. (*See* Guest, Murphy, Bodnar, Ware, and Seegers), 152*
SEGERS, M., VASTASAEGER, M., AND DENOLIN, H. Intraventricular conduction defects, 944*
SEGERS, MARCEL. Determination of the levo- and dextrocardiogram, 751
SEGRE, G. On the mechanism of digitalis action, 950*
SELKURT, EWALD E. (*See* Opdyke and Selkurt), 73
SELYE, H. (*See* Dontigny, Hay, Prado, and Selye), 956*
SEWALL, S. (*See* Lichtenstein and Sewall), 458*
SHADLE, O. W. (*See* Lawson, Overbey, Moore, and Shadle), 633*
——. (*See* Overbey, Moore, Shadle, and Lawson), 633*
SHANER, G. A. (*See* Boger, Miller, Tillson, and Shaner), 955*
SHEARD, C. H. (*See* Roth and Sheard), 785*
SHEPARD, EDWARD M., AND STEWART, HAROLD J. Interpretation of the electrocardiogram in dextrocardia with situs inversus, 55
SHIPLEY, R. E. (*See* Gregg and Shipley), 631*
SHUMACKER, H. B., JR., ABRAMSON, D. I., AND LAMPERT, H. H. The use of anticoagulants in the surgery of aneurysms and arteriovenous fistulas, with particular reference to Dicumarol, 301*
SIEGMUND, O. H., NASH, V. L., AND GRANGER, H. R. The vasopressor activity of some new orally active sympathomimetic amines, 943*
SILBER, EARL N. (*See* Pellegrino and Silber), 447
SILBERT, SAMUEL. Further experience with thromboangiitis obliterans in women, 757
SIMKIN, B. (*See* Prinzmetal, Ornitz, Simkin, and Bergman), 784*
——. (*See* Prinzmetal, Simkin, Bergman, and Kruger), 790*
SIMMS, HENRY S., PARSHLEY, MARY S., PITT, RUTH B., AND FULTON, JOAN B. Further studies on the fat-depositing mechanism (Proc.), 469
SINGLETON, A. O., AND SINGLETON, A. O., JR. Cerebral hemorrhage following repair of a common carotid-internal jugular arteriovenous fistula, 789*
SINGLETON, A. O., JR. (*See* Singleton and Singleton, Jr.), 789*
SLEVIN, J. G. New test in diagnosis and surgical treatment of varicose veins, 953*
SMITH, B. C. (*See* Mufson, Quimby, and Smith), 302*
SMITH, H. W. Hypertension and urologic disease, 943*
SOBERÓN, JORGE. (*See* Sodi-Pallares, Thomsen, and Soberón), 1
SODI-PALLARES, D. (*See* Cabrera and Sodi-Pallares), 635*
SODI-PALLARES, DEMETRIO, THOMSEN, PABLO, AND SOBERÓN, JORGE. New contributions to the study of the intracavity potential in cases of right bundle bran h block in the human heart, 1
SOLWAY, A. J. L. (*See* Schlichter, Amromin, and Solway) (Proc.), 479
SORENSON, CHARLES W. (*See* Stewart, Horger, and Sorenson), 161
SPEALMAN, C. R., NEWTON, M., AND POST, R. L. Influence of environmental temperature and posture on volume and composition of blood, 153*
SPICKNALL, G. G., AND BINFORD, C. H. Healed dissecting aneurysm of the aorta with signs of aortic insufficiency, 452*
SPRAGUE, P. H. (*See* Ross and Sprague), 772
SPRITZLER, RAMON. (*See* Prinzmetal, Corday, Spritzler, and Bergman) (Proc.), 476
SPUHLER, V. O., WIESINGER, K., AND MEILI, E. Diuretic and circulating plasma volume, 788*
STADIE, W. C., AND MARSH, J. B. The effect of cytochrome C upon the metabolism of rat tissue, 155*
STAMLER, JEREMIAH. (*See* Horlich, Katz, and Stamler) (Proc.), 472
STANTON, JOSEPH R. (*See* Freis and Stanton), 723
STEAD, E. A., JR. (*See* Warren, Brannon, Weens, and Stead, Jr.), 455*
STEINER, ALFRED, DAVIDSON, J. D., AND KENDALL, FORREST E. Further studies on the production of arteriosclerosis in dogs by cholesterol and thiouracil feeding (Proc.), 477
STEINMANN, V. B., LUDI, H., AND BARBEN, H. P. Circulatory investigations resulting from drugs which paralyze the sympathetic system. I. Ergotamine (Gynergen), 787*
STEWART, HAROLD J. (*See* Shepard and Stewart), 55
——, HORGER, EUGENE L., AND SORENSON, CHARLES W. Experience with the "anoxemia test" in patients with angina pectoris and in those with atypical chest pain, 161
——, AND NEWMAN, ABBOTT, A. The amount of digitoxin (digitaline nativelle) required for adequate digitalization, 641
STICKNEY, J. C., NORTHRUP, D. W., AND VAN LIERE, E. J. Systemic blood pressure as a factor in the absorption of saline from the small intestine, 152*

STOFER, BERT E. (*See* Myers, Klein, and Stofer), 535
STOKEY, E. (*See* Lipschitz and Stokey), 792*, 952*
STONE, R. B. (*See* Makinson, Oleesky, and Stone), 788*
STUTZMAN, J. W., MURPHY, Q., ALLEN, C. R., AND MEEK, W. J. Further studies on the production of cyclopropane-epinephrine tachycardia, 311*
SUÁREZ, RAMÓN M., SANTIAGO-STEVENSON, DWIGHT, AND HERNÁNDEZ-MOKALES, FEDERICO. Electrocardiographic changes during anthiomaline treatment of schistosomiasis, 923

T

TAINSKY, IRVING A. (*See* Richter and Tainsky), 443
TAUSSIG, HELEN B. Analysis of malformations of the heart amenable to a Blalock-Taussig operation, 321
——. Diagnosis of the tetralogy of Fallot and medical aspects of the surgical treatment, 155*
TAYLOR, H. C. (*See* Munnell and Taylor), 155*
TAYLOR, H. L., HENSCHEL, A., AND KEYS, A. Cardiovascular response to posture and the problem of faintness and syncope in the semi-starved individual, 785*
TAYLOR, R. D. (*See* Corcoran, Taylor, and Page), 226
TAYLOR, ROBERT D., BIRCHALL, ROBERT, CORCORAN, A. C., AND PAGE, IRVINE H. Circulatory responses to spinal and caudal anesthesia in hypertension: relation to the effect of sympathectomy. I. Effect on arterial pressure, 221
TERRANOVA, R. (*See* Scherf, Romano, and Terranova), 241
THOMAS, W. L. (*See* Ross, Lambeth, Thomas, and Carter), 795*
THOMPSON, C. W. (*See* Maynard and Thompson), 305*
THOMSEN, PABLO. (*See* Sodi-Pallares, Thomsen, and Soberón), 1
THORDARSON, O. Clinical study on the relative incidence of congenital heart disease, 150*
TILLOTSON, K. J. (*See* Altschule and Tillotson), 788*
TILLSON, E. K. (*See* Boger, Miller, Tillson, and Shaner), 955*
TRAUM, AARON H. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox), 334
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Cont'd), 481
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Concl'd), 683
TRUMP, RUTH. (*See* Kyser and Trump), 133
TUCKER, HERBERT DE N. (*See* Hull, Tucker, and Weilbaecher, Jr.), 135

U

UHLEY, M. N., AND WILBURNE, M. The effect of intravenous procaine on the electrocardiogram of the dog, 576
UNGAR, H. Diffuse interstitial myocarditis in a case of epidemic encephalitis, 458*
UNGERLEIDER, HARRY E., AND GUBNER, RICHARD. Clinical significance of blood cholesterol (Proc.), 474

V

VASTESAEGER, M. (*See* Segers, Vastesaeger, and Denolin), 944*
VERNIORY, A. (*See* Lequine, Denolin, and Verniory), 949*
VINCENT, D. The effect of certain cardiac glucosides on serum cholinesterase, 945*

W

WAGNER, B. M. Penicillin therapy in subacute bacterial endocarditis, 303*
WALCOTT, W. W. (*See* Root, Walcott, and Gregerson), 632*
WALKER, W. J. (*See* Massey and Walker), 786*
WANG, S. C., AND BORISON, H. L. An analysis of the carotid sinus cardiovascular reflex mechanism, 461*
——, AND ——. Decussation of the pathways in the carotid sinus cardiovascular reflex: an example of the principle of convergence, 460*
WARE, A. G. (*See* Guest, Murphy, Bodnar, Ware, and Seegers), 152*
WARREN, J. V., BRANNON, E. S., WEENS, H. S., AND STEAD, E. A., JR. Effect of increasing the blood volume and right atrial pressure on the circulation of normal subjects by intravenous infusions, 455*
WARTMAN, W. B., AND HELLERSTEIN, H. K. The incidence of heart disease in 2,000 consecutive autopsies, 317*
WATERS, L. L., AND MCALLISTER, W. B. Reactions of the coronary arteries of the dog following injury by allylamine (Proc.), 475
WATSON, W. L. Pulmonary arteriovenous aneurysm, 301*
WEENS, H. S. (*See* Warren, Brannon, Weens, and Stead, Jr.), 455*
WEGRIA, R., AND BOYLE, M. N. Correlation between the effect of quinidine sulfate on the heart and its concentration in the blood plasma, 793*
WEILBAECHER, J. O., JR. (*See* Hull, Tucker, and Weilbaecher, Jr.), 135
WELCH, K. J. Failure of the peritoneal-button operation for ascites, report of two cases, 313*
WELFARE, C. R. (*See* McMillan and Welfare), 314*
WENDHOLZ, F., AND GRAYSON, C. Roentgen demonstration of calcifications in the interventricular septum in cases of heart block, 309*
WENDKOS, MARTIN H. (*See* Logue and Wendkos), 587
WERKÖ, L. (*See* Motley, Cournand, Werkö, Himmelstein, and Dresdale), 152*
WERKÖ, LARS. (*See* Ferrer, Harvey, Werkö, Dresdale, Cournand, and Richards, Jr.), 316

WESSLER, S. (*See* Blumgart, Freedberg, Zoll, Lewis, and Wessler), 13
WESTMAN, C. (*See* Biorck, Gohle, and Westman), 948*
WIESINGER, K. (*See* Spuhler, Wiesinger, and Meili), 788*
WIGGERS, C. J., LEVY, M. N., AND GRAHAM, G. Regional intrathoracic pressures and their bearing on calculation of effective venous pressures, 631*
WILBURNE, M., SCHLICHTER, J. G., GROSSMAN, M., AND CISNEROS, F. The use of acetylcholine in the objective determination of circulation time and the fractionation of the vascular bed traversed, 153*
——. (*See* Uhley and Wilburne), 576
WILCOX, BLANCHE B. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox), 334
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Cont'd), 481
——. (*See* Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox) (Concl'd), 683
WILENS, S. L., ELSTER, S., AND BAKER, J. Glomerular lipoidosis in intercapillary glomerulosclerosis (Proc.), 478
——. The relationship of chronic alcoholism to atherosclerosis, 315*
WILKINSON, CHARLES F., JR., BLECHA, ELMIRA, AND REIMER, ANN. The relationship between dietary composition and the blood cholesterol level (Proc.), 472
WINKLER, A. W. (*See* Danowski, Winkler, and Elkington), 308*
WHITE, H. L., HEINBECKER, P., AND ROLF, D. Endocrine influences on cardiac output and oxygen consumption in dogs, 633*
WOOD, EARL H. (*See* Montgomery, Jr., Wood, Burchell, Dry, Parker, and Helmholz, Jr.), 668
——. (*See* Pollack and Wood), 899
WRIGHT, IRVING S., MARPLE, CHARLES D., AND BECK, DOROTHY FAHS. Report of the committee for the evaluation of anticoagulants in the treatment of coronary thrombosis with myocardial infarction, 301

Y

YATER, WALLACE M., TRAUM, AARON H., BROWN, WILSON G., FITZGERALD, RICHARD P., GEISLER, MURRAY A., AND WILCOX, BLANCHE B. Coronary artery disease in men eighteen to thirty-nine years of age, 334
——, ——, ——, ——, ——, AND ——. Coronary artery disease in men eighteen to thirty-nine years of age (Cont'd), 481
——, ——, ——, ——, ——, AND ——. Coronary artery disease in men eighteen to thirty-nine years of age (Concl'd), 683

Z

ZEMAN, FREDERIC D., AND SCHENCK, MAX. The clinical diagnosis of arteriosclerosis with particular reference to the use of the roentgen ray (Proc.), 480
ZILLIACUS, H. (*See* Maeck and Zilliacus), 790*
ZOHMAN, B. L. (*See* Russek and Zohman), 459*
ZOLL, P. M. (*See* Blumgart, Freedberg, Zoll, Lewis, and Wessler), 13

# SUBJECT INDEX*


A

Abdominal symptoms in sudden acute heart conditions, 306*
Abscess, cerebral; complication of congenital cardiac disease (Fallot's tetralogy), 301*
Acetylcholine, effect of calcium on cardiovascular stimulation produced by, 793*, 953*
  use of, in objective determination of circulation time and fractionation of vascular bed traversed, 153*
Adrenalin-induced hyperglycemia, effect of anoxia on, 150*
Alcoholism, chronic, relationship of, to atherosclerosis, 315*
Alloxan diabetes in rabbit, inhibition of experimental cholesterol atherosclerosis by (Duff and McMillan) (Proc.), 469
Allylamine, reactions of coronary arteries of dog following injury by (Waters and McAllister) (Proc.), 475
American Heart Association, Inc., 158, 318, 463, 638, 796, 957
    governing bodies of, 318
    recommendations of Research Policy Committee, 463
  Society for the Study of Arteriosclerosis, proceedings of, 469
    program of annual meeting of, 466
Amines, sympathomimetic, orally active, some new, vasopressor activity of, 943*
Aminophylline, intravenous, effect of, on capacity for effort without pain in patients with angina of effort (Bakst et al.), 527
Analgesic drugs, effects of, upon excised frog and terrapin cardiac vagus nerve, 950*
Anastomoses, arteriovenous, in liver, spleen, and lungs, 784*
Anatomical axis, longitudinal, of ventricles, can it be estimated from electrocardiogram? (Hyman et al.), 906
Anemia, chronic, clinical significance of cardiac and respiratory adjustments in, 795*
Anesthesia in surgery of patent ductus arteriosus, 316*
  spinal and caudal, in hypertension, circulatory responses to: relation to effect of sympathetctomy. I. Effect on arterial pressure (Taylor et al.), 221
    II. Effect on renal function (Corcoran et al.), 226
Aneurysm, arteriovenous, pulmonary, 301*
  congenital, of aortic sinus, 305*
  dissecting, healed, of aorta with signs of aortic insufficiency, 452*
  of coronary arteries (Scott), 403
Aneurysms and arteriovenous fistulas, use of anticoagulants in surgery of, with particular reference to Dicumarol, 301*
  dissecting, of aorta (Schlichter et al.) (Proc.), 479
  syphilitic, Cellophane treatment of, with report of results in six cases (Poppe), 252
  true, of mitral valve in subacute bacterial endocarditis, 304*
Angina of effort, effect of intravenous aminophylline on capacity for effort without pain in patients with (Bakst et al.), 527
  pectoris, experience with "anoxemia test" in patients with, and in those with atypical chest pain (Stewart et al.), 161
    myocardial infarction and, during serum sickness, 151*
    S-T changes, and subendocardic infarctions, contribution to study of, 636*
    treatment of, by reduction of basal metabolism, 791*
    vitamin E in, 788*
Anginal pain, coronary occlusion with myocardial infarction following cholecystectomy for relief of, in patients with cholelithiasis (Roth), 939
Angiospasm, cerebral, (vascular encephalopathy), papaverine in, 459*
"Anoxemia test," experience with, in patients with angina pectoris and in those with atypical chest pain (Stewart et al.), 161
  transitory apnea in man induced by breathing mixture rich in oxygen during state of, 949*
Anoxia, acute, induced, influence of short periods of, upon pulmonary artery pressure in man, 152*
  and cytochrome C, oxygen content of coronary venous blood as affected by (Eckenhoff and Hafkenschiel), 893
  anoxemic, effects of, on excitability, conduction, and refractoriness, of mammalian cardiac muscle, 152*
  effect of, on adrenalin-induced hyperglycemia, 150*
  effects of, on retinal vessels and retinal arterial pressure, 313*
  on cause of cardiac acceleration during, 946*
Anthiomaline treatment of schistosomiasis, electrocardiographic changes during (Suárez et al.), 923
Anticoagulants in treatment of coronary thrombosis with myocardial infarction, report of committee for evaluation of (Wright et al.), 801


*An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

Anticoagulants—Cont'd
use of, in surgery of aneurysms and arteriovenous fistulas, with particular reference to Dicumarol, 301*
Aorta, abdominal, ligation and division of, for metallic embolus from heart, 950*
dissecting aneurysms of (Schlichter et al.) (Proc.), 479
effect of blood cholesterol disorders on coronary arteries and (Morrison and Gonzales) (Proc.), 473
embolism at bifurcation of (Morest and Rubin), 277
high ventricular septal defect with slight dextroposition of, (Eisenmenger type), which presented clinical features of patent ductus arteriosus (Hurst and Schemm), 144
Aortic bifurcation, syndrome of thrombotic obliteration of, 951*
insufficiency, healed dissecting aneurysm of aorta with signs of, 452*
sinus, congenital aneurysm of, 305*
Aortography, thoracic, 948*
Apnea, transitory, in man induced by breathing mixture rich in oxygen during state of anoxemia, 949*
Arterial blood, rate of disappearance of dye T-1824 from, 633*
disease, obliterating, exercise test in, 151*
of upper extremity following severe urticaria, 151*
sympathectomy for; indications and contraindications, 635*
studies on relationship of diet and renal insufficiency to (Holman) (Proc.), 476
hypertension, cerebral vascular changes in, (Scheinker) (Proc.), 470
obstruction, pulmonary, acute, experimental study of, with special reference to precordial electrocardiogram (Flasher et al.), 882
occlusion, mesenteric, superior,—recovery without resection, 787*
oxygen saturation at rest and during exercise in congenital heart disease, continuous observations of (Montgomery, Jr., et al.), 668
pressure, effect on (I); circulatory responses to spinal and caudal anesthesia in hypertension: relation to effect of sympathectomy (Taylor et al.), 221
Arteries, coronary, aneurysm of (Scott), 403
nonatheromatous lesions of, 303*
of dog, reactions of, following injury by allylamine (Waters and McAllister) (Proc.), 475
Arteriography of limbs, 154*
Arteriosclerosis, clinical diagnosis of (Davis) (Proc.), 473
with particular reference to use of roentgen ray (Zeman and Schenck) (Proc.), 480
evaluation of thyroid function in older individuals with various degrees of (Kountz et al.), 475
further studies on production of, in dogs by cholesterol and thiouracil feeding (Steiner et al.) (Proc.), 477
Arteriosclerosis—Cont'd
new experiments in (Altschul) (Proc.), 480
obliterans rationale, sympathectomy for, and results (Blain, III, et al.) (Proc.), 477
peripheral, lumbar ganglionectomy in (Gerber et al.) (Proc.), 478
spontaneously occurring, of chicken, effect of low-fat diet on (Horlick et al.) (Proc.), 472
Arteriovenous aneurysm, pulmonary, 301*
fistula, common carotid-internal jugular, cerebral hemorrhage following repair of, 789*
Artery disease, coronary, in men eighteen to thirty-nine years of age (Yater et al.), 334, 481, 683
pressure, pulmonary, influence of short periods of induced acute anoxia upon, in man, 152*
Ascites, failure of peritoneal-button operation for, report of two cases, 313*
Atheromatous plaques, development, of following production of intimal atherosclerosis by intravenous injection of colloidal cholesterol into rabbits (Bevins et al.) (Proc.), 473
Atherosclerosis, aortic, absorption of, by choline feeding (Morrison and Rossi) (Proc.), 479
cholesterol, experimental, inhibition of, by alloxan diabetes in rabbit (Duff and McMillan) (Proc.), 469
experimental, prevention of, by choline feedings (Morrison and Rossi) (Proc.), 479
intimal, development of atheromatous plaques following production of, by intravenous injections of colloidal cholesterol into rabbits (Bevans et al.) (Proc.), 473
relationship of chronic alcoholism to, 315*
Atresia, tricuspid, congenital, associated with interauricular septal defects (Miale et al.), 438
Atrial infarction with diagnostic electrocardiographic findings (Hellerstein), 422
septal defect, differentiation of patent ductus arteriosus and, 634*
Atrioventricular block complete, in diphtheritic myocarditis, 786*
canal, incomplete division of, with patent interatrial foramen primum (persistent common atrioventricular ostium) (Rogers and Edwards), 28
excitation, anomalous, intermittent, (Wolff-Parkinson-White syndrome) septal infarction with complete heart block and: histologic demonstration of right lateral bundle (Levine and Burge, Jr.), 431
Auricle, kymographic studies of function of, 949*
Auricular fibrillation, chronic, 314*
pre-excitation and, 461*
flutter and auricular fibrillation, experimental studies on (Scherf et al.), 241
clinical, proof of its occurrence; discussion of circus movement, 635*

Auriculoventricular heart block, mechanism of irregular sinus rhythm in (Roth and Kisch), 257
A-V block, partial, and duodenal ulcer, 948*
Axis, anatomical, longitudinal, of ventricles, can it be estimated from electrocardiogram? (Hyman et al.), 906
deviation, effect of posture upon, in human bundle branch block (Jones and Feil), 739
in human bundle branch block (Jones and Feil), 98

B

Bacteremia following dental extraction, effect of penicillin on, 302*
Bacterial endocarditis (Cecil et al.), 934
subacute, hyperthermia caused by penicillin-heparin in treatment of, 790*
penicillin therapy in, 303*
treatment of, 453*
true aneurysms of mitral valve in, 304*
Barbitalized dogs, mixing of cells, plasma, and dye T-1824 in cardiovascular system of, 633*
Basal metabolism, treatment of angina pectoris by reduction of, 791*
Bifurcation of aorta, embolism at (Morest and Rubin), 277
Bile, excretion of blue dye, T-1824, in, 632*
Biochemical and hemodynamic changes following subcutaneous injection of glucose solution, 308*
Blalock-Taussig operation, analysis of malformations of heart amenable to (Taussig), 321
Blood cholesterol level, relationship between dietary composition and (Wilkinson, Jr., et al.) (Proc.), 472
composition of, influence of environmental temperature and posture on volume and, 153*
constituents, certain, influence of thyroid status on electrocardiogram and, of sheep, 785*
flow, coronary, and cardiac oxygen metabolism, effect of nikethamide on, 156*
through vessels in vein walls, effects of venous endothelium on alterations in, and possible relation to thrombosis, 462*
plasma, correlation between effect of quinidine sulfate on heart and its concentration in, 793*
platelets, observations on part played by vasoconstrictor substance of, in mechanism of vascular spasm, 307*
pressure, basal, effect of thiocyanate on, 791*
effect of tetraethylammonium chloride on, before and after sympathectomy for hypertension, 793*
leucocyte concentration, smooth and cardiac muscle activity: physiological effects of plasma protein, 152*
recording of, from left auricle and pulmonary veins in human subjects with interauricular septal defects, 151*
Blood Pressure—Cont'd
systemic, as factor in absorption of saline from small intestine, 152*
studies on cholesterol content of coronary arteries and, in acute coronary thrombosis (Morrison et al.) (Proc.), 474
volume and right atrial pressure, effect of increasing, on circulation of normal subjects by intravenous infusions, 455*
circulatory corpuscle and, in case of patent ductus arteriosus before and after ligation, 150*
studies of, in tetralogy of Fallot and in other types of congenital heart disease, 308*
Blue dye, T-1824, excretion of, in bile, 632*
Bradycardia, extreme (Doane and Krasnoff), 777
Bronchiogenic carcinoma, undiagnosed, case report of mechanical right heart failure from extension of, 312*
Bundle branch block, human, effect of posture upon axis deviation in (Jones and Feil), 739
on axis deviation in (Jones and Feil), 98
right, in human heart, new contributions to study of intracavity potential in cases of (Sodi-Pallares et al.), 1
lateral, right, histologic demonstration of: septal infarction with complete heart block and intermittent anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) (Levine and Burge, Jr.), 431

C

Calcification of myocardium, 302*
Calcifications, cardiac annular and valvular (leaflet), 794*
roentgen demonstration of, in interventricular septum in cases of heart block, 309*
Calcium, effect of, on cardiovascular stimulation produced by acetylcholine, 793*, 953*
Canal, atrioventricular, incomplete division of, with patent interatrial foramen primum (persistent common atrioventricular ostium) (Rogers and Edwards), 28
Capillaries, cerebral, alterations of, in early stage of arterial hypertension, 784*
Carcinoma, bronchiogenic, undiagnosed, case report of mechanical right heart failure from extension of, 310*
Cardiac acceleration during anoxia, on cause of, 946*
and respiratory adjustments in chronic anemia, clinical significance of, 795*
apex formed by right or left ventricular myocardium, identical electrocardiograms with, 949*
disease, congenital, (Fallot's tetralogy), complication of; cerebral abscess, 301*
dynamics, endo-sinusal hypotension and, in sympathectomized and in completely denervated heart of dogs (III); heart and carotid sinus, 946*

Cardiac—Cont'd
lesions of acute disseminated lupus erythematosus, 786*
output and oxygen consumption in dogs, endocrine influences on, 633*
of dog, effects of muscle trauma and of hemorrhage upon, 632*
role of carotid sinus and cardio-aortic region in reflex regulation of, 949*
resuscitation, 947*
Cardio-aortic region, role of carotid sinus and, in reflex regulation of cardiac output, 949*
Cardiotoxic lesions of digitalis in dog, further studies on effect of papaverine upon (Kyser and Trump), 133
Cardiovascular disorder with peripheral neuritis, six cases of, 310*
reflex, carotid sinus, decussation of pathways in: example of principle of convergence, 460*
mechanism, carotid sinus, analysis of, 461*
system as effector organ in psychosomatic phenomena, 943*
of barbitalized dogs, mixing of cells, plasma, and dye T-1824 in, 633*
Carditis, allergic, pericarditis, and pleurisy, 456*
Caronamide: plasma concentrations, urinary recoveries, and dosage, 955*
Carotid sinus and cardio-aortic region, role of, in reflex regulation of cardiac output, 949*
cardiovascular reflex, decussation of pathways in: example of principle of convergence, 460*
mechanism, analysis of, 461*
heart and; II and III, 946*
stimulation, hemiplegia following (Brannon), 299
Caudal anesthesia, spinal and, in hypertension, circulatory responses to: relation to effect of sympathectomy; I. Effect on arterial pressure (Taylor et al.), 221
II. Effect on renal function (Corcoran et al.), 226
Cellophane treatment of syphilitic aneurysms with report of results in six cases (Poppe), 252
Cerebral abscess; complication of congenital cardiac disease (Fallot's tetralogy), 301*
capillaries, alterations of, in early stage of arterial hypertension, 784*
hemorrhage following repair of common carotid-internal jugular arteriovenous fistula, 789*
swelling, hypertensive, characteristic clinicopathologic syndrome, 457*
vascular changes in arterial hypertension (Scheinker) (Proc.), 470
Chest leads, multiple, in myocardial infarction, diagnostic value of pattern $T_1$ lower than $T_3$ ($T_1 < T_3$) compared with information yielded by (Dressler and Roesler), 115
Chest—Cont'd
pain, atypical, experience with "anoxemia test" in patients with angina pectoris and in those with (Stewart et al.), 161
Childhood, first ten years of rheumatic infection in (Ash), 89
Cholecystectomy for relief of anginal pain in patient with cholelithiasis, coronary occlusion with myocardial infarction following (Roth), 939
Cholelithiasis, coronary occlusion with myocardial infarction following cholecystectomy for relief of anginal pain in patient with (Roth), 939
Cholesterol and thiouracil feeding, further studies on production of arteriosclerosis in dogs by (Steiner et al.) (Proc.), 477
atherosclerosis, experimental, inhibition of, by alloxan diabetes in rabbit (Duff and McMillan) (Proc.), 469
blood, clinical significance of (Ungerleider and Gubner) (Proc.), 474
disorders, effect of, on coronary arteries and aorta (Morrison and Gonzales) (Proc.), 473
levels, changes in, in patients with coronary occlusion following choline therapy (Morrison et al.) (Proc.), 474
colloidal, development of atheromatous plaques following production of intimal atherosclerosis by intravenous infusions of, into rabbits (Bevans et al.) (Proc.), 473
content of coronary arteries and blood in acute coronary thrombosis, study on (Morrison et al.) (Proc.), 474
level, blood, relationship between dietary composition and (Wilkinson, Jr., et al.) (Proc.), 472
some aspects of intermediary metabolism of (Bloch) (Proc.), 471
Choline feeding, absorption of aortic atherosclerosis by (Morrison and Rossi) (Proc.), 479
feedings, prevention of experimental atherosclerosis by (Morrison and Rossi) (Proc.), 479
therapy, changes in blood cholesterol levels in patients with coronary occlusion following (Morrison et al.) (Proc.), 474
Chorea, Sydenham's syndrome for differential diagnosis, 154*
Circulation, collateral, of normal human heart by coronary perfusion with radioactive erythrocytes and glass spheres, studies on, 790*
new method for study of: radiocardiography (Prinzmetal et al.) (Proc.), 476
some effects of quinidine sulfate on heart and, in man (Ferrer et al.), 816
time and fractionation of vascular bed traversed, use of acetylcholine in objective determination of, 153*

Circulatory changes, renal and cardiac, influence of sulfhydryl compounds on diuresis and, caused by mersalyl, 452*
investigations resulting from drugs which paralyze sympathetic system. I. Ergotamine (Gynergen), 787*
responses to spinal and caudal anesthesia in hypertension: relation to effect of sympathectomy. I. Effect on arterial pressure (Taylor et al.), 221
II. Effect on renal function (Corcoran et al.), 226
Circus movement, discussion of; proof of its occurrence in clinical auricular flutter, 635*
Conduction defects, intraventricular, 944*
intraventricular, supernormal phase of (Scherf and Scharf), 621
Convergence, example of principle of: decussation of pathways in carotid sinus cardiovascular reflex, 460*
Convulsions, electrically induced, mechanisms underlying pulmonary and cardiac complications of, 788*
Coronary arteries and aorta, effect of blood cholesterol disorders on (Morrison and Gonzales) (Proc.), 473
and blood, studies on cholesterol content of, in acute coronary thrombosis (Morrison et al) (Proc.), 474
aneurysm of (Scott), 403
nonatheromatous lesions of: progress of medical science, 303*
of dog, reactions of, following injury by allylamine (Waters and McAllister) (Proc.), 475
in men eighteen to thirty-nine years of age (Yater et al.), 334, 481, 683
insufficiency, apparent, ergotamine and, 629*
stress and electrocardiogram in induced hypoxemia test for (Burchell et al.), 373
occlusion, acute, experimental, effect of Dicumarol on heart in (Blumgart et al.), 13
following choline therapy, changes in blood cholesterol levels in patients with (Morrison et al.) (Proc.), 474
study of alleged intercoronary reflexes following (Opdyke and Selkurt), 73
with myocardial infarction following cholecystectomy for relief of anginal pain in patient with cholelithiasis (Roth), 939
thrombosis, hypertension and (Paterson and Holmes) (Proc.), 470
with myocardial infarction, report of committee for evaluation of anticoagulants in treatment of (Wright et al.), 801
venous blood, oxygen content of, as affected by anoxia and cytochrome C (Eckenhoff and Hafkenschiel), 893
Corpuscle, circulatory, and blood volume in case of patent ductus arteriosus before and after ligation, 150*
Cyclopropane-epinephrine tachycardia, further studies on production of, 311*
Cytochrome C, effect of, upon metabolism of rat tissue, 155*
oxygen content of coronary venous blood as affected by anoxia and (Eckenhoff and Hafkenschiel), 893

D

Dental extraction, effect of penicillin on bacteremia following, 302*
Dextrocardia and septal defects, 949*
with situs inversus, interpretation of electrocardiogram in (Shepard and Stewart), 55
Dextrocardiogram, levo- and, detemination of (Segers), 751
Diabetes, alloxan, inhibition of experimental cholesterol atherosclerosis by, in rabbit (Duff and McMillan) (Proc.), 469
Dicumarol, effect of, on heart in experimental acute coronary occlusion (Blumgart et al.), 13
poisoning, 454*
therapy in seventy-five consecutive cases, detailed study of: acute myocardial infarction (Greisman and Marcus), 600
use of anticoagulants in surgery of aneurysms and arteriovenous fistulas, with particular reference to, 301*
Diet and renal insufficiency, studies on relationship of, to arterial disease (Holman) (Proc.), 476
Dietary composition and blood cholesterol level, relationship between (Wilkinson, Jr., et al.) (Proc.), 472
Digitaline nativelle, digitoxin, amount of, required for adequate digitalization (Stewart and Newman), 641
Digitalis action, on mechanism of, 950*
further studies on effect of papaverine upon cardiotoxic lesions of, in dog (Kyser and Trump), 133
glycosides, further experiments in attempt to locate site of emetic action of, 156*
influence of muscular exercise on tolerance of, in guinea pigs, 948*
on behavior of serum cholinesterase in cardiac patients treated with, 309*
toxicity, hitherto undescribed neurological manifestations of (Batterman and Gutner), 582
Digitoxin (Digitaline nativelle), amount of, required for adequate digitalization (Stewart and Newman), 641
Diphtheria, fatal, myocardial changes in, 953*
Diphtheritic myocarditis, complete atrioventricular block in, 786*
Diuresis and renal and cardiac circulatory changes caused by mersalyl, influence of sulfhydryl compounds on, 452*, 950*
Diuretic action of formoguanamine in normal persons, 792*, 952*

E

Edema, uremic, of lungs, 310*

Electric shock, ventricular fibrillation of long duration abolished by, 156*

Electrical effects of injury at various myocardial locations (Hellerstein and Katz), 184
manometer, portable, suitable for continuous indication of peripheral venous pressures (Pollack and Wood), 899

Electrically induced convulsions, mechanisms underlying cardiac complications of, 788*

Electrocardiogram and certain blood constituents of sheep, influence of thyroid status on, 785*
can longitudinal anatomical axis of ventricles be estimated from? (Hyman et al.), 906
evaluation of precordial leads of, in obesity (Jaffe et al.), 911
in mitral stenosis with special regard to its development, 461*
interpretation of, in dextrocardia with situs inversus (Shepard and Stewart), 55
of dog, effect of intravenous procaine on (Uhley and Wilburne), 576
precordial, experimental study of acute pulmonary arterial obstruction with special reference to (Flasher et al.), 882
stress and, in induced hypoxemia test for coronary insufficiency (Burchell et al.), 373

Electrocardiograms, identical, with cardiac apex formed by right or left ventricular myocardium, 949*
precordial, false abnormality of, due to effect of changes of potential at remote electrode (Hull et al.), 135

Electrocardiographic and clinical studies on certain types of myocardial infarction: supra-apical, endocardial, epicardial, lateral, and anterolateral infarction, 629*
and pathologic findings in anteroseptal infarction, correlation of (I) (Myers et al.), 535
(II) (Myers et al.), 838
changes during anthiomaline treatment of schistosomiasis (Suárez et al.), 923
in typhoid fever and their reversibility following niacin treatment (Rachmilewitz and Braun), 284
findings, diagnostic, atrial infarction with (Hellerstein), 422

Electroconvulsive treatment, transient hemiplegia following, 952*

Electrode, remote, false abnormality of precordial electrocardiograms due to effect of changes of potential at (Hull et al.), 135

Electronic stethoscope, multiple channel, for teaching and demonstration (Butterworth and Poindexter), 112

Electrovectography, two- and three-dimensional, in man, 150*

Embolism at bifurcation of aorta (Morest and Rubin), 277
paradoxical, case of (Ross and Sprague), 772
pulmonary, 789*

Embolus, metallic, from heart, ligation and division of abdominal aorta for, 950*

Emetic action of digitalis gycosides, further experiments in attempt to locate site of, 156*

Emphysema, mediastinal, spontaneous, recurrent, simulating myocardial infarction (Pellegrino and Silber), 447

Encephalitis, epidemic, diffuse interstitial myocarditis in case of, 458*

Endocarditis, bacterial (Cecil et al.), 934
subacute, true aneurysms of mitral valve in, 304*

Endocrine influences on cardiac output and oxygen consumption in dogs, 633*

Endothelium, venous, effects of, on alterations in blood flow through vessels in vein walls, and possible relation to thrombosis, 462*

Ergotamine and apparent coronary insufficiency, 629*
(Gynergen) (I); circulatory investigations resulting from drugs which paralyze sympathetic system, 787*

Erythrocytes, radioactive, and glass spheres, studies on collateral circulation of normal human heart by coronary perfusion with, 790*

Ether, pulmonary and cerebral fat embolism following intravenous administration of, therapeutically, 458*

Evans blue, combination of, with plasma protein: its significance in capillary permeability studies, blood dye disappearance curves, and its use as protein tag, 632*

Excitation, atrioventricular, anomalous, intermittent, (Wolff-Parkinson-White syndrome), septal infarction with complete heart block and: histologic demonstration of right lateral bundle (Levine and Burge, Jr.), 431

Extrasystoles, auricular and ventricular, first heart sound in, 630*

Extremities, lower, in infants, gangrene of (Richter and Tainsky), 443
of normal individuals, maintenance of vasodilation of, for prolonged period by ingestion of two to four substantial meals in close succession, 785*

F

Faintness and syncope in semi-starved individual, problem of, cardiovascular response to posture and, 785*

Fat-depositing mechanism, further studies on (Sims et al.) (Proc.), 469

Fat embolism, pulmonary and cerebral, following intravenous administration of ether therapeutically, 458*
low, diet, effect of, on spontaneously occurring arteriosclerosis of chicken (Horlick et al.) (Proc.), 472
Fibrillation, auricular, chronic, 314*
experimental studies on auricular flutter and (Scherf et al.), 241
pre-excitation and, 461*
Fistulas, arteriovenous, aneurysms and, use of anticoagulants in surgery of, with particular reference to Dicumarol, 301*
Fluid volumes, available and interstitial, of normal children, 634*
Flutter, auricular, and auricular fibrillation, experimental studies on (Scherf et al.), 241
Foramen primum, interatrial, patent, (persistent common atrioventricular ostium) incomplete division of atrioventricular canal with (Rogers and Edwards), 28
Formoguanamine, diuretic action of, in normal persons, 792*, 952*
Fractionation, circulation time and, of vascular bed traversed, use of acetylcholine in objective determination of, 153*

G

Gangrene of lower extremities in infants (Richter and Tainsky), 443
Glass spheres, studies on collateral circulation of normal human heart by coronary perfusion with radioactive erythrocytes and, 790*
Glomerulonephritis, acute and subacute, myocarditis associated with (Gore and Saphir), 390
Glomerulosclerosis, intercapillary, glomerular lipoidosis in (Wilens et al.) (Proc.), 478
Glucose solution, biochemical and hemodynamic changes following subcutaneous injection of, 308*
Glycosides, cardiac, certain, effect of, on serum cholinesterase, 945*
determination of therapeutic irregularity and lethal doses of, in heart-lung preparation of dog, 452* 950*

H

Heart, analysis of malformations of, amenable to Blalock-Taussig operation (Taussig), 321
and carotid sinus; II and III, 946*
and circulation, some effects of quinidine sulfate on, in man (Ferrer et al.), 816
and pericardium, further observations of penetrating wounds of, 311*
block, auriculoventricular, mechanism of irregular sinus rhythm in (Roth and Kisch), 257
complete and intermittent anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome), septal
Heart block—Cont'd
infarction with: histologic demonstration of right lateral bundle (Levine and Burge, Jr.), 431
roentgen demonstration of calcifications in interventricular septum in cases of, 309*
completely denervated, of dogs, endo-sinusal hypotension and cardiac dynamics in sympathectomized, and in (III); heart and carotid sinus, 946*
conditions, acute, sudden, abdominal symptoms in, 306*
disease, congenital, continuous observations of arterial oxygen saturation at rest and during exercise in (Montgomery, Jr., et al.), 668
clinical study on relative incidence of, 150*
studies of blood volume in tetralogy of Fallot and in other types of, 308*
incidence of, in 2,000 consecutive autopsies, 317*
effect of Dicumarol on, in experimental acute coronary occlusion (Blumgart et al.), 13
failure, case of reversible papilloedema due to, 454*
hypertensive, tetraethyl ammonium bromide in hypertension and, 453*
postpartal, acute, 312*
right, mechanical, from extension of undiagnosed bronchiogenic carcinoma, case report of, 312*
human, new contributions to study of intracavity potential in cases of right bundle branch block in (Sodi-Pallares et al.), 1
ligation and division of abdominal aorta for metallic embolus from, 950*
muscle, electrical characteristics of injuries to, 153*
neoplastic metastasis to (Lefkovits), 610
occult injuries to, 316*
removal of foreign bodies from pericardium and; moving picture demonstration, 947*
sound, first, in auricular and ventricular extrasystoles, 630*
spontaneous rupture of papillary muscle of, 955*
studies of venous drainage of, 631*
Heart-lung preparation of dog, determination of therapeutic irregularity and lethal doses of cardiac glycosides in, 452*, 950*
Hemangioma, cavernous, of lung, 956*
Hemiplegia following carotid sinus stimulation (Brannon), 299
transient, following electroconvulsive treatment, 952*
Hemodynamic changes, biochemical and, following subcutaneous injection of glucose solution, 308*
Hemorrhage, effects of muscle trauma and of, upon cardiac output of dog, 632*
Herapin, action of, on experimental venous thrombosis, 312*
in treatment of toxemia of pregnancy, 790*

Hepatic vein catheterization flow in pregnancy, 155*
Hyperglycemia, adrenalin induced, effect of anoxia on, 150*
Hypertension and allied cases, sympathetic nerve block in, 306*
and coronary thrombosis (Paterson and Holmes) (Proc.), 470
and hypertensive heart failure, tetraethyl ammonium bromide in, 453*
and unilateral kidney disease, 306*
and urologic disease, 943*
arterial alterations of cerebral capillaries in early stage of, 784*
cerebral vascular changes in (Scheinker) (Proc.), 470
circulatory responses to spinal and caudal anesthesia in: relation to effect of sympathectomy. I. Effect on arterial pressure (Taylor et al.), 221
II. Effect on renal function (Corcoran et al.), 226
effect of tetraethylammonium chloride on blood pressure before and after sympathectomy for, 793*
essential, clinical evaluation of veratrum viride in treatment of (Freis and Stanton), 723
sympathectomy in, 946*
treatment of, with vitamin K, 945*
experimental, effect of pregnancy on course of, 634*
fifty-four deaths occurring in pregnant patients who had, 795*
heredity in, 459*
hormonal, and nephrosclerosis as influenced by diet, 956*
paroxysmal, due to chromaffin adrenal tumor, electrocardiographic changes in, 150*
Hyperthermia caused by penicillin-heparin in treatment of subacute bacterial endocarditis, 790*
Hypotension, endo-sinusal, and right ventricular pressure (II); heart and carotid sinus, 946*
Hypoxemia test, induced, for coronary insufficiency, stress and electrocardiogram in (Burchell et al.), 373

I

Iliofemoral thrombophlebitis, nontraumatic, bilateral, in child (Myers and Artsis), 295
Infancy, cardiac murmurs in, 787*
Infant, newborn, myocardial infarction in, 154*
Infants, gangrene of lower extremities in (Richter and Tainsky), 443
Infarction, anteroseptal, correlation of electrocardiographic and pathologic findings in (I) (Myers et al.), 535
atrial, with diagnostic electrocardiographic findings (Hellerstein), 422
myocardial, acute: detailed study of Dicumarol therapy in seventy-five consecutive cases (Greisman and Marcus), 600
Infarction, myocardial—Cont'd
and angina pectoris during serum sickness, 151*
diagnostic value of pattern $T_1$ lower than $T_3$ ($T_1 < T_3$) compared with information yielded by multiple chest leads in (Dressler and Roesler), 115
recurrent spontaneous mediastinal emphysema simulating (Pellegrino and Silber), 447
septal, with complete heart block and intermittent anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome): histologic demonstration of right lateral bundle (Levine and Burge, Jr.), 431
Infarcts, anterolateral, large, correlation of electrocardiographic and pathologic findings in (II) (Myers et al.), 838
Infection, rheumatic, in childhood, first ten years of (Ash), 89
Insufficiency, coronary, stress and electrocardiogram in induced hypoxemia test for (Burchell et al.), 373
Interatrial foramen primum, patent (persistent common atrioventricular ostium), incomplete division of atrioventricular canal with (Rogers and Edwards), 28
Interauricular and interventricular septal defects, congenital tricuspid atresia associated with, (Miale et al.), 438
septal defects, recording of blood pressure from left auricle and pulmonary veins in human subjects with, 151*
Intercoronary reflexes, alleged, following coronary occlusion, study of (Opdyke and Selkurt), 73
Interventricular septal defects, interauricular and, congenital tricuspid atresia associated with (Miale et al.), 438
septum, in cases of heart block, roentgen demonstration of calcifications in, 309*
Intracavity potential, new contributions to study of, in cases of right bundle branch block in human heart (Sodi-Pallares et al.), 1
Intravenous infusions, effect of increasing blood volume and right atrial pressure on the circulation of normal subjects by, 455*
Intraventricular conduction, supernormal phase of (Scherf and Scharf), 621

K

Kidney disease, unilateral, hypertension and, 306*
K-strophanthin, significance of speed of injection for therapeutic effect of, 944*
Kymographic studies of function of auricle, 949*

L

Leads, precordial, of electrocardiogram in obesity, evaluation of (Jaffe et al.), 911

Leucocyte concentration, blood pressure, and smooth and cardiac muscle activity: physiological effects of plasma protein, 152*
Levo- and dextrocardiogram, determination of (Segers), 751
Limbs, arteriography of, 154*
Lipoidosis, glomerular, in intercapillary glomerulosclerosis (Wilens et al.) (Proc.), 478
Liver blood flow in pregnancy—hepatic vein catheterization, 155*
spleen, and lungs, arteriovenous anastomoses in, 784*
Longitudinal anatomical axis of ventricles, can it be estimated from electrocardiogram? (Hyman et al.), 906
Lumbar ganglionectomy in peripheral arteriosclerosis (Gerber et al.) (Proc.), 478
Lung, cavernous hemangioma of, 956*
Lungs, arteriovenous anastomoses in liver, spleen, and, 784*
uremic edema of, 310*
Lupus erythematosus and allied conditions, pathogenesis of, 785*
disseminated, acute, cardiac lesions of, 786*

M

Malaria tertiana, myocardial affection in, 154*
Manometer, electrical, portable, suitable for continuous indication of peripheral venous pressures (Pollack and Wood), 899
Men eighteen to thirty-nine years of age, coronary artery disease in (Yater et al.), 334, 481, 683
Mersalyl, influence of sulfhydryl compounds on diuresis and renal and cardiac circulatory changes caused by, 452*, 950*
Metabolism, intermediary, of cholesterol, some aspects of (Bloch) (Proc.), 471
of rat tissue, effect of cytochrome C upon, 155*
oxygen, cardiac, effect of nikethamide on coronary blood flow and, 156*
Metastasis, neoplastic, to heart (Lefkovits), 610
Mitral stenosis, electrocardiogram in, with special regard to its development, 461*
valve, true aneurysms of, in subacute bacterial endocarditis, 304*
Murmurs, cardiac, in infancy, 787*
Muscle activity, smooth and cardiac, blood pressure, leucocyte concentration, and: physiological effects of plasma protein, 152*
auricular, of turtle, augmentation of effects of vagal stimulation upon, by veratrine and sulfocyanate, 945*
cardiac, hypersensitivity of, to potassium ion following administration of veratrine and sulfocyanate after complete atropinization, 945*
mammalian, effects of anoxemic anoxia on excitability, conduction, and refractoriness of, 152*
Muscle, heart—Cont'd
heart, electrical characteristic of injuries to, 153*
papillary, of heart, spontaneous rupture of, 955*
trauma, effects of, and of hemorrhage upon cardiac output of dog, 632*
Muscular exercise, influence of, on tolerance of digitalis in guinea pigs, 948*
Myocardial affection in malaria tertiana, 154*
changes in fatal diphtheria, 953*
infarction, acute: detailed study of Dicumarol therapy in seventy-five consecutive cases (Greisman and Marcus), 600
coronary occlusion with, following cholecystectomy for relief of anginal pain in patient with cholelithiasis (Roth), 939
diagnostic value of pattern $T_1$ lower than $T_3$ ($T_1 < T_3$) compared with information yielded by multiple chest leads in (Dressler and Roesler), 115
electrocardiographic and clinical studies on certain types of: supra-apical, endocardial, epicardial, lateral, and anterolateral infarction, 629*
in newborn infant, 154*
recurrent spontaneous mediastinal emphysema simulating (Pellegrino and Silber), 447
report of committee for evaluation of anticoagulants in treatment of coronary thrombosis with (Wright et al.), 801
locations, various, electrical effects of injury at (Hellerstein and Katz), 184
Myocarditis associated with acute and subacute glomerulonephritis (Gore and Saphir), 390
diphtheritic, complete atrioventricular block in, 786*
interstitial, diffuse, in case of epidemic encephalitis, 458*
rheumatic, latent, 157*
typhoid, electrocardiographic study of, 944*
virus, 783*
Myocardium after sulfonamide therapy, 304*
calcification of, 302*
ventricular, right or left, identical electrocardiograms with cardiac apex formed by, 949*

N

Nephrosclerosis, hormonal hypertension and, as influenced by diet, 956*
Nerve block, sympathetic, in hypertension and allied cases, 306*
Neuritis, peripheral, six cases of cardiovascular disorder with, 310*
Neurological manifestations, hitherto undescribed, of digitalis toxicity (Batterman and Gutner), 582
Niacin treatment, electrocardiographic changes in typhoid fever and their reversibility following (Rachmilewitz and Braun), 284
Nikethamide, effect of, on coronary blood flow and cardiac oxygen metabolism, 156*

O

Obesity, evaluation of precordial leads of electrocardiogram in (Jaffe et al.), 911
Occlusion, arterial, mesenteric, superior,—recovery without resection, 787*
coronary, acute, experimental, effect of Dicumarol on heart in (Blumgart et al.), 13
study of alleged intercoronary reflexes following (Opdyke and Selkurt), 73
Oxygen, arterial, saturation at rest and during exercise in congenital heart disease, continuous observations of (Montgomery, Jr., et al.). 668
consumption, endocrine influences on cardiac output and, in dogs, 633*
content of coronary venous blood as affected by anoxia and cytochrome C (Eckenhoff and Hafkenschiel), 893
transitory apnea in man induced by breathing mixture rich in, during state of anoxemia, 949*

P

Papaverine, further studies on effect of, upon cardiotoxic lesions of digitalis in dog (Kyser and Trump), 133
in cerebral angiospasm (vascular encephalopathy), 459*
Papilloedema, reversible, due to heart failure, case of, 454*
Patent ductus arteriosus and atrial septal defect, differentiation of, 634*
anesthesia in surgery of, 316*
before and after ligation, circulatory corpuscle and blood volume in case of, 150*
cause for re-establishment of communication following ligation of, 451*
high ventricular septal defect with slight dextroposition of aorta (Eisenmenger type) which presented clinical features of (Hurst and Schemm), 144
prognosis of, 631*
Pattern $T_1$ lower than $T_3$ ($T_1 < T_3$), diagnostic value of, compared with information yielded by multiple chest leads in myocardial infarction (Dressler and Roesler), 115
Penicillin, effect of, on bacteremia following dental extraction, 302*
oral, in prophylaxis of recurrent rheumatic fever, 157*
therapy in subacute bacterial endocarditis, 303*
Penicillin-heparin, hyperthermia caused by, in treatment of subacute bacterial endocarditis, 790*
Periarteritis nodosa with recovery; report of unusual case apparently due to sensitivity to sulfadiazine, 451*
Pericarditis, acute, of benign type (Logue and Wendkos), 587
allergic carditis and pleurisy, 456*
Pericardium and heart, removal of foreign bodies from: moving picture demonstration, 947*
heart, and further observations on penetrating wounds of, 311*
Peripheral arteriosclerosis, lumbar ganglionectomy in (Gerber et al.) (Proc.), 478
vascular system, use of radioactive sodium as guide to efficiency of drugs used in treatment of diseases of, 302*
Peritoneal-button operation for ascites, failure of, report of two cases, 313*
Plasma protein, combination of Evans blue with: its significance in capillary permeability studies, blood dye disappearance curves, and its use as protein tag, 632*
physiological effects of: blood pressure, leucocyte concentration, smooth and cardiac muscle activity, 152*
volume, diuretic and circulating, 788*
Pleurisy, allergic carditis, pericarditis and, 456*
Postpartal heart failure, acute, 312*
Posture, cardiovascular response to, and problem of faintness and syncope in semi-starved individual, 785*
effect of, upon axis deviation in human bundle branch block (Jones and Feil), 739
influence of environmental temperature and, on volume and composition of blood, 153*
Potassium ion, hypersensitivity of cardiac muscle to, following administration of veratrine and sulfocyanate after complete atropinization, 945*
Potential, false abnormality of precordial electrocardiograms due to effect of changes of, at remote electrode (Hull et al.), 135
intracavity, new contributions to study of, in cases of right bundle branch block in human heart (Sodi-Pallares et al.), 1
Precordial electrocardiogram, experimental study of acute pulmonary arterial obstruction, with special reference to (Flasher et al.), 882
electrocardiogram, false abnormality of, due to effect of changes of potential at remote electrode (Hull et al.), 135
leads of electrocardiogram in obesity, evaluation of (Jaffe et al.), 911
Pregnancy, acute rheumatism in, 792*
effect of, on course of experimental hypertension, 634*
heparin in treatment of toxemia of, 790*
liver blood flow in—hepatic vein catheterization, 155*
nine-year follow-up in cases of toxemia of, 790*
Pregnant patients who had hypertension, fifty-four deaths occurring in, 795*
Pressure, atrial, right, effect of increasing blood volume and, on circulation of normal subjects by intravenous infusions, 455*

Pressures, intrathoracic, regional, and their bearing on calculation of effective venous pressures, 631*
venous, peripheral, portable electrical manometer suitable for continuous indication of (Pollack and Wood), 899
Procaine, intravenous, effect of, on electrocardiogram of dog (Uhley and Wilburne), 576
Protein, Raynaud's syndrome originating from reversible precipitation of, 153*, 460*
Psychosomatic phenomena, cardiovascular system as effector organ in, 943*
Pulmonary arterial obstruction, acute, experimental study of, with special reference to precordial electrocardiogram (Flasher et al.), 882
embolism, 789*
infarction, thoracic tenderness in, 788*
stenosis, congenital, (tetralogy of Fallot), hitherto unrecognized tendency to development of widespread pulmonary vascular obstruction in patients with, 458*

Q

Q-T interval, simple method of determining abnormalities of (Goldberger), 141
Quinidine sulfate, effect of, on heart and its concentration in blood plasma, correlation between, 793*
some effects of, on heart and circulation in man (Ferrer et al.), 816

R

Radioactive sodium, use of, as guide to efficiency of drugs used in treatment of diseases of peripheral vascular system, 302*
Radiocardiography: new method for study of circulation (Prinzmetal et al.) (Proc.), 476
Raynaud's syndrome originating from reversible precipitation of protein, 153*, 460*
Recommendations of Research Policy Committee. I. Training and support of men of outstanding ability, 463
II. General principals regarding grants-in-aid, 464
III. Fluid grants, 464
IV. Composition and duties of Research Allocation Committee, 464
V. Alterations in research allocation policy, 465
Reflexes, intercoronary, alleged, following coronary occlusion, study of (Opdyke and Selkurt), 73
Renal diseases: some facts and problems, 455*
function, effect on (II); circulatory responses to spinal and caudal anesthesia in hypertension: relation to effect of sympathectomy (Corcoran et al.), 226
insufficiency, studies on relationship of diet and, to arterial disease (Holman) (Proc.), 476
Respiratory, cardiac and, adjustments in chronic anemia, clinical significance of, 795*
Resuscitation, cardiac, 947*
Retinal vessels and retinal arterial pressure, effects of anoxia on, 313*
Rheumatic fever, recurrent, oral penicillin in prophylaxis of, 157*
infection in childhood, first ten years of (Ash), 89
myocarditis, latent, 157*
Rheumatism, acute, in pregnancy, 792*
Rice diet, treatment of hypertensive vascular disease with, 794*
Roentgen ray, clinical diagnosis of arteriosclerosis with particular reference to use of (Zeman and Schenck) (Proc.), 480

S

Saline, systemic blood pressure as factor in absorption of, from small intestine, 152*
Schistosomiasis, electrocardiographic changes during anthiomaline treatment of (Suárez et al.), 923
Septal defect, ventricular, high, with slight dextroposition of aorta (Eisenmenger type) which presented clinical features of patent ductus arteriosus (Hurst and Schemm), 144
defects, dextrocardia and, 949*
Serum cholinesterase, effect of certain cardiac glycosides on, 945*
on behavior of, in cardiac patients treated with digitalis, 309*
sickness, myocardial infarction and angina pectoris during, 151*
Sinus, aortic, congenital aneurysm of, 305*
rhythm, irregular, mechanism of, in auriculoventricular heart block (Roth and Kisch), 257
stimulation, carotid, hemiplegia following (Brannon), 299
Situs inversus, interpretation of electrocardiogram in dextrocardia with (Shepard and Stewart), 55
Sodium, radioactive, use of, as guide to efficiency of drugs used in treatment of diseases of peripheral vascular system, 302*
Spasm, vascular, observations on part played by vasoconstrictor substance of blood platelets in mechanism of, 307*
Spinal and caudal anesthesia in hypertension, circulatory responses to: relation to effect of sympathectomy. I. Effect on arterial pressure (Taylor et al.), 221
II. Effect on renal function (Corcoran et al.), 226
Spleen, liver, and lungs, arteriovenous anastomoses in, 784*

S-T changes, angina pectoris, and subendocardic infarctions, contributions to study of, 636*
Stethoscope, electronic, multiple channel, for teaching and demonstration (Butterworth and Poindexter), 112
Stress and electrocardiogram in induced hypoxemia test for coronary insufficiency (Burchell et al.), 373
Subendocardic infarctions, contribution to study of S-T changes, angina pectoris, and, 636*
Sulfadiazine, report of unusual case apparently due to sensitivity to; periarteritis nodosa with recovery, 451*
Sulfhydryl compounds, influence of, on diuresis and renal and cardiac circulatory changes caused by mersalyl, 452*, 950*
Sulfocyanate, augmentation of effects of vagal stimulation upon auricular muscle of turtle by veratrine and, 945*
hypersensitivity of cardiac muscle to potassium ion following administration of veratrine and, after complete atropinization, 945*
Sulfonamide therapy, myocardium after, 304*
Sympathectomy for arteriosclerosis obliterans rationale and results (Blain, III, et al.) (Proc.), 477
for obliterative arterial disease; indications and contraindications, 635*
in essential hypertension, 946*
relation to effect of: circulatory responses to spinal and caudal anesthesia in hypertension. I. Effect on arterial pressure (Taylor et al.), 221
II. Effect on renal function (Corcoran et al.), 226
Sympathetic system, circulatory investigations resulting from drugs which paralyze. I. Ergotamine (Gynergen), 787*
Syncope, problem of faintness and, in semistarved individual, cardiovascular response to posture and, 785*
studies of. IV. Biologic interpretation of vasodepressor syncope, 309*
Syphilitic aneurysms, Cellophane treatment of, with report of results in six cases (Poppe), 252

T

$T_1$ lower than $T_3$ pattern, ($T_1 < T_3$) diagnostic value of, compared with information yielded by multiple chest leads in myocardial infarction (Dressler and Roesler), 115
T-1824, dye, mixing of cells, plasma, and, in cardiovascular system of barbitalized dogs, 633*
rate of disappearance of, from arterial blood, 633*
excretion of, in bile, 632*
mixing curve, re-evaluation of, 633*
Tachycardia, cyclopropane-epinephrine, further studies of production of, 311*
paroxysmal, repetitive, 629*
Temperature, environmental, and posture, influence of, on volume and composition of blood, 153*
Tetraethyl ammonium bromide in hypertension and hypertensive heart failure, 453*
Tetraethylammonium chloride, 952*
effect of, on blood pressure before and after sympathetcomy for hypertension, 793*
$(N(C_2H_5)_4NCl)$; acute and chronic toxicity in experimental animals, 792*
Tetralogy of Fallot and its surgical treatment, 459*
diagnosis of, and medical aspects of surgical treatment, 155*
studies of blood volume in, and in other types of congenital heart disease, 308*
Thiocyanate, effect of, on basal blood pressure, 791*
Thiouracil, cholesterol and, feeding, further studies on production of arteriosclerosis in dogs by (Steiner et al.) (Proc.), 477
Thoracic tenderness in pulmonary infarction, 788*
Thromboangiitis obliterans in women, further experience with (Silbert), 757
Thrombophlebitis, iliofemoral, nontraumatic, bilateral, in child (Myers and Artsis), 295
Thrombosis, coronary, acute, studies on cholesterol content of coronary arteries and blood in (Morrison et al.) (Proc.), 474
venous, experimental, action of heparin on, 312*
Thrombotic obliteration of aortic bifurcation, syndrome of, 951*
Thyroid function in older individuals with various degrees of arteriosclerosis, evaluation of (Kountz et al.) (Proc.), 475
status, influence of, on electrocardiogram and certain blood constituents of sheep, 785*
Toxemia of pregnancy, heparin in treatment of, 790*
nine-year follow-up in cases of, 790*
Toxicity, digitalis, hitherto undescribed neurological manifestations of (Batterman and Gutner), 582
Tumor, adrenal, chromaffin, electrocardiographic changes in paroxysmal hypertension due to, 150*
Typhoid fever, electrocardiographic changes in, and their reversibility following niacin treatment (Rachmilewitz and Braun), 284
myocarditis, electrocardiographic study of, 944*

U

Ulcer, duodenal, partial A-V block and, 948*
Urologic disease, hypertension and, 943*
Urticaria, severe, obliterating arterial disease of upper extremity following, 151*

V

Vagal stimulation, augmentation of effects of, upon auricular muscle of turtle by veratrine and sulfacyanate, 945*
Vagus nerve, cardiac, excised frog and terrapin, effects of analgesic drugs upon, 950*
reaction of peripheral vascular system of dog to stimulation of central end of, 946*
Varicose ulcer, treatment of, 954*
veins, new test in diagnosis and surgical treatment of, 953*
Vascular changes, cerebral, in arterial hypertension (Scheinker) (Proc.), 470
disease, hypertensive, diagnosis and natural history of, 457*
treatment of, with rice diet, 794*
obstruction, pulmonary, widespread, hitherto unrecognized tendency to development of, in patients with congenital pulmonary stenosis (tetralogy of Fallot), 458*
spasm, observations on part played by vasoconstrictor substance of blood platelets in mechanism of, 307*
system, peripheral, of dog, reaction of, to stimulation of central end of vagus nerve, 946*
Vasodilation of extremities of normal individuals for prolonged period by ingestion of two to four substantial meals in close succession, maintenance of, 785*
Vasopressor activity of some new orally active sympathomimetic amines, 943*
Venous blood, coronary, oxygen content of, as affected by anoxia and cytochrome C (Eckenhoff and Hafkenschiel), 893
drainage, of heart, studies of, 631*
Venous—Cont'd
pressures, effective, regional intrathoracic pressures and their bearing on calculation of, 631*
peripheral, portable electrical manometer suitable for continuous indication of (Pollack and Wood), 899
Ventricles, can longitudinal anatomical axis of, be estimated from electrocardiogram (Hyman et al.), 906
Ventricular fibrillation of long duration abolished by electric shock, 156*
septal defect, high, with slight dextroposition of aorta (Eisenmenger type) which presented clinical features of patent ductus arteriosus (Hurst and Schemm), 144
tachycardia, paroxysmal, with special reference to treatment, 636*
Veratrine and sulfocyanate, augmentation of effects of vagal stimulation upon auricular muscle of turtle by, 945*
hypersensitivity of cardiac muscle to potassium ion following administration of, after complete atropinization, 945*
Veratrum viride in treatment of essential hypertension, clinical evaluation of (Freis and Stanton), 723
Virus myocarditis, 783*
Vitamin E in angina pectoris, 788*
K, treatment of essential hypertension with, 945*

W

Wolff-Parkinson-White syndrome, 308*
Women, further experience with thromboangiitis obliterans in (Silbert), 757
Wounds, penetrating, of heart and pericardium, further observation on, 311*

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